FILE 'CAPLUS' ENTERED AT 17:54:34 ON 10 APR 2002
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FILE 'USPATFULL' ENTERED AT 17:54:34 ON 10 APR 2002

=> s l3 and orphenadrin?
L20 2 L3 AND ORPHENADRIN?

=> dup rem l20
PROCESSING COMPLETED FOR L20
L21 2 DUP REM L20 (0 DUPLICATES REMOVED)

=> d l21 abs ibib kwic 1-2

L21 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
AB Comparison of 7-hydroxylation of coumarin, a CYP2A6 substrate, in human and African green and cynomolgus monkey liver microsomes was made by an HPLC assay with UV detection. In human liver microsomes, the Km and Vmax values for the metabolic conversion were 2.1 .mu.M and 0.79 nmol/mg/min, resp. While African green monkey showed Km and Vmax values of 2.7 .mu.M and 0.52 nmol/mg/min, which were similar to human, higher Km and Vmax values were found in cynomolgus monkey. Coumarin 7-hydroxylation in human and African green monkey was selectively inhibited by **methoxsalen** and pilocarpine (CYP2A6 inhibitors) but not by other inhibitors, i.e. .alpha.-naphthoflavone (CYP1A1), **orphenadrine** (CYP2B6), sulfaphenazole (CYP2C9), quinidine (CYP2D6), and ketoconazole (CYP3A4). Immunoinhibition results supported CYP2A6 involvement in human and its homolog in monkey in coumarin 7-hydroxylation, as only anti-CYP2A6, but not CYP2B1, CYP2C13, CYP2D6, CYP2E1, or CYP3A antibodies, inhibited this conversion. African green monkey was similar to human in catalytic activity of coumarin 7-hydroxylation and response to CYP2A6 inhibitors or antibody inhibition. However, the monkey CYP2A6 is not identical to the human in that Ki values were different, and differences were obsd. with some CYP2A6 inhibitors, such as nicotine and **methoxsalen**, suggesting that, under some circumstances, studies of nicotine kinetics and drug taking behavior in monkey may not be comparable to human.
ACCESSION NUMBER: 1998:150136 CAPLUS
DOCUMENT NUMBER: 128:164257
TITLE: Comparison of CYP2A6 catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes
AUTHOR(S): Li, Yan; Li, Ning Yuan; Sellers, Edward M.
CORPORATE SOURCE: Dep. Pharmacology, Medicine, Psychiatry, Univ. Toronto, Toronto, ON, M5S 1A8, Can.
SOURCE: Eur. J. Drug Metab. Pharmacokinet. (1997), 22(4), 295-304
CODEN: EJDPD2; ISSN: 0378-7966
PUBLISHER: Medecine et Hygiene
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Comparison of 7-hydroxylation of coumarin, a CYP2A6 substrate, in human and African green and cynomolgus monkey liver microsomes was made by an HPLC assay with UV detection. In human liver microsomes, the Km and Vmax values for the metabolic conversion were 2.1 .mu.M and 0.79 nmol/mg/min, resp. While African green monkey showed Km and Vmax values of 2.7 .mu.M

L4 ANSWER 8 OF 64 CAPLUS COPYRIGHT 2002 ACS

AB The title method using psycho- and reflexotherapy was proposed. With the purpose of enhancing of efficiency of therapy 5-6 h before the start of the reflexotherapeutic procedure oral cavity was irrigated by 1.0% soln. of pilocarpine hydrochloride and Et chloride with simultaneous inhalation of Et chloride vapors.

ACCESSION NUMBER: 1994:238085 CAPLUS
DOCUMENT NUMBER: 120:238085
TITLE: Method of abstinence syndrome treatment in tobacco dependence
INVENTOR(S): Garnitskij, Sergej P.; Shuteeva, Larisa V.
PATENT ASSIGNEE(S): "Know How" Cooperative Medical Center, USSR
SOURCE: U.S.S.R. From: Izobreteniya 1993, (11), 11. CODEN: URXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Russian
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
	SU 1803032	A1	19930323	SU 1990-4859314	19900322	<--
PI	SU 1803032 A1 **19930323**					
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	SU 1803032	A1	19930323	SU 1990-4859314	19900322	<--

ST **tobacco dependence** abstinence syndrome reflexotherapy psychotherapy; **pilocarpine** hydrochloride **tobacco dependence** abstinence syndrome; Et chloride **tobacco dependence** abstinence syndrome

IT 54-71-7, **Pilocarpine** hydrochloride 75-00-3, Ethyl chloride
RL: BIOL (Biological study)
(in **tobacco dependence** abstinence syndrome treatment)

=>

→ administer pilocarpine HCL 1% soln to the tongue (of human)
→ quantity 0.2-0.5 ml over course of 1-2 seconds

L19 ANSWER 4 OF 42 CAPLUS COPYRIGHT 2002 ACS

AB Nine org. solvents and 47 commonly used P 450 substrates and inhibitors were examd. for their effects on coumarin 7-hydroxylase (CYP2A6) activity in human liver microsomes. Of the nine org. solvents examd. (final concn. 1%, vol./vol.), only methanol did not inhibit the 7-hydroxylation of coumarin (0.5 to 50 .mu.M) by human liver microsomes. Dioxane and THF, which are structurally related to coumarin, were the most inhibitory solvents examd. Although the rates of coumarin 7-hydroxylation varied enormously among nine samples of human liver microsomes and cDNA-expressed CYP2A6 (Vmax = 179 to 2470 pmol/mg protein/min), the Km for coumarin 7-hydroxylation was fairly const. (ranging from 0.50 to 0.70 .mu.M). The following chems. caused little or no inhibition of CYP2A6 as defined by a Ki > 200 .mu.M: caffeine, chlorzoxazone, cimetidine, dextromethorphan, diazepam, diclofenac, erythromycin, ethynylestradiol, ethynyltestosterone, fluconazole, furafylline, furfural, hexobarbital, itraconazole, mephenytoin, methimazole, metronidazole, naringenin, naringin, nifedipine, norfloxacin, norgestrel, **orphenadrine**, quinidine, papaverine, phenacetin, pyrimethamine, ranitidine, spironolactone, sulfaphenazole, sulfinpyrazone, testosterone, tolbutamide, troleandomycin, and warfarin. In other words, these chems., at a final concn. of 100 .mu.M, failed to inhibit CYP2A6 when the concn. of coumarin was equal to Km (0.50 .mu.M). The following chems. were classified as strong inhibitors of CYP2A6 (defined by Ki < 200 .mu.M): clotrimazole, diethyldithiocarbamate, ellipticine, ketoconazole, 8-methoxypsoralen, 4-methylpyrazole, metyrapone, miconazole, .alpha.-naphthoflavone, **nicotine**, p-nitrophenol, and tranylcypromine. The potency with which each chem. inhibited the 7-hydroxylation of coumarin was independent of which sample of human liver microsomes was studied. One of the most potent inhibitors of coumarin 7-hydroxylase was 8-methoxypsoralen (methoxsalen), which was detd. to be a mechanism-based inhibitor (suicide substrate) of CYP2A6 (kinactivation 0.5 min-1). With the exception of 8-methoxypsoralen, preincubation of human liver microsomes and NADPH with the aforementioned inhibitors did not increase their ability to inhibit CYP2A6. The most potent competitive inhibitor of CYP2A6 was tranylcypromine (Ki = 0.04 .mu.M). Several of the chems. that strongly inhibited CYP2A6, such as ketoconazole and tranylcypromine, are often used with the intention of selectively inhibiting human P 450 enzymes other than CYP2A6.

ACCESSION NUMBER: 1997:287113 CAPLUS
DOCUMENT NUMBER: 126:273360
TITLE: Inhibition of coumarin 7-hydroxylase activity in human liver microsomes
AUTHOR(S): Draper, Alison J.; Madan, Ajay; Parkinson, Andrew
CORPORATE SOURCE: Dep. Pharmacol., Toxicol., Therapeutics, Cent. Environ. Occupational Health, Univ. Kansas Med. Cent., Kansas City, KS, 66160-7417, USA
SOURCE: Arch. Biochem. Biophys. (1997), 341(1), 47-61
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Arch. Biochem. Biophys. (1997), 341(1), 47-61
CODEN: ABBIA4; ISSN: 0003-9861
AB Nine org. solvents and 47 commonly used P 450 substrates and inhibitors were examd. for their effects on coumarin 7-hydroxylase (CYP2A6) activity in human liver microsomes. Of the nine org. solvents examd. (final concn. 1%, vol./vol.), only methanol did not inhibit the 7-hydroxylation of

coumarin (0.5 to 50 .mu.M) by human liver microsomes. Dioxane and THF, which are structurally related to coumarin, were the most inhibitory solvents examd. Although the rates of coumarin 7-hydroxylation varied enormously among nine samples of human liver microsomes and cDNA-expressed CYP2A6 (Vmax = 179 to 2470 pmol/mg protein/min), the Km for coumarin 7-hydroxylation was fairly const. (ranging from 0.50 to 0.70 .mu.M). The following chems. caused little or no inhibition of CYP2A6 as defined by a Ki > 200 .mu.M: caffeine, chlorzoxazone, cimetidine, dextromethorphan, diazepam, diclofenac, erythromycin, ethynylestradiol, ethynyltestosterone, fluconazole, furafylline, furfural, hexobarbital, itraconazole, mephenytoin, methimazole, metronidazole, naringenin, naringin, nifedipine, norfloxacin, norgestrel, **orphenadrine**, quinidine, papaverine, phenacetin, pyrimethamine, ranitidine, spironolactone, sulfaphenazole, sulfinpyrazone, testosterone, tolbutamide, troleandomycin, and warfarin. In other words, these chems., at a final concn. of 100 .mu.M, failed to inhibit CYP2A6 when the concn. of coumarin was equal to Km (0.50 .mu.M). The following chems. were classified as strong inhibitors of CYP2A6 (defined by Ki < 200 .mu.M): clotrimazole, diethyldithiocarbamate, ellipticine, ketoconazole, 8-methoxypsoralen, 4-methylpyrazole, metyrapone, miconazole, .alpha.-naphthoflavone, **nicotine**, p-nitrophenol, and tranylcypromine. The potency with which each chem. inhibited the 7-hydroxylation of coumarin was independent of which sample of human liver microsomes was studied. One of the most potent inhibitors of coumarin 7-hydroxylase was 8-methoxypsoralen (methoxsalen), which was detd. to be a mechanism-based inhibitor (suicide substrate) of CYP2A6 (kinactivation 0.5 min-1). With the exception of 8-methoxypsoralen, preincubation of human liver microsomes and NADPH with the aforementioned inhibitors did not increase their ability to inhibit CYP2A6. The most potent competitive inhibitor of CYP2A6 was tranylcypromine (Ki = 0.04 .mu.M). Several of the chems. that strongly inhibited CYP2A6, such as ketoconazole and tranylcypromine, are often used with the intention of selectively inhibiting human P 450 enzymes other than CYP2A6.

IT 50-12-4, Mephenytoin 52-01-7, Spironolactone 54-11-5, **Nicotine** 54-36-4, Metyrapone 56-29-1, Hexobarbital 56-54-2, Quinidine 57-63-6, Ethynylestradiol 57-96-5, Sulfinpyrazone 58-08-2, Caffeine, biological studies 58-14-0, Pyrimethamine 58-22-0, Testosterone 58-74-2, Papaverine 60-56-0, Methimazole 62-44-2, Phenacetin 64-17-5, Ethanol, biological studies 64-77-7, Tolbutamide 67-56-1, Methanol, biological studies 67-63-0, 2-Propanol, biological studies 67-64-1, Acetone, biological studies 67-68-5, DMSO, biological studies 68-12-2, DMF, biological studies 75-05-8, Acetonitrile, biological studies 81-81-2, Warfarin 83-98-7, **Orphenadrine** 95-25-0, Chlorzoxazone 98-01-1, Furfural, biological studies 100-02-7, p-Nitrophenol, biological studies 109-99-9, Tetrahydrofuran, biological studies 114-07-8, Erythromycin 123-91-1, Dioxane, biological studies 125-71-3, Dextromethorphan 147-84-2, biological studies 155-09-9, Tranylcypromine 298-81-7, 8-Methoxypsoralen 434-03-7 439-14-5, Diazepam 443-48-1, Metronidazole 480-41-1, Naringenin 519-23-3, Ellipticine 526-08-9, Sulfaphenazole 604-59-1, .alpha.-Naphthoflavone 2751-09-9, Troleandomycin 6533-00-2, Norgestrel 7554-65-6, 4-Methylpyrazole 10236-47-2, Naringin 15307-86-5, Diclofenac 21829-25-4, Nifedipine 22916-47-8, Miconazole 23593-75-1, Clotrimazole 51481-61-9, Cimetidine 65277-42-1, Ketoconazole 66357-35-5, Ranitidine 70458-96-7, Norfloxacin 80288-49-9, Furafylline 84625-61-6, Itraconazole 86386-73-4, Fluconazole

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (coumarin hydroxylase inhibition in human liver microsomes)

=> d l19 abs ibib kwic 1-42

L19 ANSWER 1 OF 42 CAPLUS COPYRIGHT 2002 ACS

AB Comparison of 7-hydroxylation of coumarin, a CYP2A6 substrate, in human and African green and cynomolgus monkey liver microsomes was made by an HPLC assay with UV detection. In human liver microsomes, the Km and Vmax values for the metabolic conversion were 2.1 .mu.M and 0.79 nmol/mg/min, resp. While African green monkey showed Km and Vmax values of 2.7 .mu.M and 0.52 nmol/mg/min, which were similar to human, higher Km and Vmax values were found in cynomolgus monkey. Coumarin 7-hydroxylation in human and African green monkey was selectively inhibited by methoxsalen and pilocarpine (CYP2A6 inhibitors) but not by other inhibitors, i.e. .alpha.-naphthoflavone (CYP1A1), **orphenadrine** (CYP2B6), sulfaphenazole (CYP2C9), quinidine (CYP2D6), and ketoconazole (CYP3A4). Immunoinhibition results supported CYP2A6 involvement in human and its homolog in monkey in coumarin 7-hydroxylation, as only anti-CYP2A6, but not CYP2B1, CYP2C13, CYP2D6, CYP2E1, or CYP3A antibodies, inhibited this conversion. African green monkey was similar to human in catalytic activity of coumarin 7-hydroxylation and response to CYP2A6 inhibitors or antibody inhibition. However, the monkey CYP2A6 is not identical to the human in that Ki values were different, and differences were obsd. with some CYP2A6 inhibitors, such as **nicotine** and methoxsalen, suggesting that, under some circumstances, studies of **nicotine** kinetics and drug taking behavior in monkey may not be comparable to human.

ACCESSION NUMBER: 1998:150136 CAPLUS
DOCUMENT NUMBER: 128:164257
TITLE: Comparison of CYP2A6 catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes
AUTHOR(S): Li, Yan; Li, Ning Yuan; Sellers, Edward M.
CORPORATE SOURCE: Dep. Pharmacology, Medicine, Psychiatry, Univ. Toronto, Toronto, ON, M5S 1A8, Can.
SOURCE: Eur. J. Drug Metab. Pharmacokinet. (**1997**), 22(4), 295-304
CODEN: EJDPD2; ISSN: 0378-7966
PUBLISHER: Medecine et Hygiene
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Eur. J. Drug Metab. Pharmacokinet. (**1997**), 22(4), 295-304
CODEN: EJDPD2; ISSN: 0378-7966

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human in that Ki values were different, and differences were obsd. with some CYP2A6 inhibitors, such as **nicotine** and methoxsalen, suggesting that, under some circumstances, studies of **nicotine** kinetics and drug taking behavior in monkey may not be comparable to human.

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IT 92-13-7, Pilocarpine **298-81-7, Methoxsalen**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(selective inhibition of coumarin 7-hydroxylation by)

L21 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS

AB Nine org. solvents and 47 commonly used P 450 substrates and inhibitors were examd. for their effects on coumarin 7-hydroxylase (CYP2A6) activity in human liver microsomes. Of the nine org. solvents examd. (final concn. 1%, vol./vol.), only methanol did not inhibit the 7-hydroxylation of coumarin (0.5 to 50 .mu.M) by human liver microsomes. Dioxane and THF, which are structurally related to coumarin, were the most inhibitory solvents examd. Although the rates of coumarin 7-hydroxylation varied enormously among nine samples of human liver microsomes and cDNA-expressed CYP2A6 (Vmax = 179 to 2470 pmol/mg protein/min), the Km for coumarin 7-hydroxylation was fairly const. (ranging from 0.50 to 0.70 .mu.M). The following chems. caused little or no inhibition of CYP2A6 as defined by a Ki > 200 .mu.M: caffeine, chlorzoxazone, cimetidine, dextromethorphan, diazepam, diclofenac, erythromycin, ethynylestradiol, ethynyltestosterone, fluconazole, furafylline, furfural, hexobarbital, itraconazole, mephenytoin, methimazole, metronidazole, naringenin, naringin, nifedipine, norfloxacin, norgestrel, **orphenadrine**, quinidine, papaverine, phenacetin, pyrimethamine, ranitidine, spironolactone, sulfaphenazole, sulfinpyrazone, testosterone, tolbutamide, troleandomycin, and warfarin. In other words, these chems., at a final concn. of 100 .mu.M, failed to inhibit CYP2A6 when the concn. of coumarin was equal to Km (0.50 .mu.M). The following chems. were classified as strong inhibitors of CYP2A6 (defined by Ki < 200 .mu.M): clotrimazole, diethyldithiocarbamate, ellipticine, ketoconazole, 8-methoxypsoralen, 4-methylpyrazole, metyrapone, miconazole, .alpha.-naphthoflavone, nicotine, p-nitrophenol, and tranylcypromine. The potency with which each chem. inhibited the 7-hydroxylation of coumarin was independent of which sample of human liver microsomes was studied. One of the most potent inhibitors of coumarin 7-hydroxylase was 8-methoxypsoralen (**methoxsalen**), which was detd. to be a mechanism-based inhibitor (suicide substrate) of CYP2A6 (kinactivation 0.5 min-1). With the exception of 8-methoxypsoralen, preincubation of human liver microsomes and NADPH with the aforementioned inhibitors did not increase their ability to inhibit CYP2A6. The most potent competitive inhibitor of CYP2A6 was tranylcypromine (Ki = 0.04 .mu.M). Several of the chems. that strongly inhibited CYP2A6, such as ketoconazole and tranylcypromine, are often used with the intention of selectively inhibiting human P 450 enzymes other than CYP2A6.

ACCESSION NUMBER: 1997:287113 CAPLUS
DOCUMENT NUMBER: 126:273360
TITLE: Inhibition of coumarin 7-hydroxylase activity in human liver microsomes
AUTHOR(S): Draper, Alison J.; Madan, Ajay; Parkinson, Andrew
CORPORATE SOURCE: Dep. Pharmacol., Toxicol., Therapeutics, Cent. Environ. Occupational Health, Univ. Kansas Med. Cent., Kansas City, KS, 66160-7417, USA
SOURCE: Arch. Biochem. Biophys. (1997), 341(1), 47-61
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nine org. solvents and 47 commonly used P 450 substrates and inhibitors were examd. for their effects on coumarin 7-hydroxylase (CYP2A6) activity in human liver microsomes. Of the nine org. solvents examd. (final concn. 1%, vol./vol.), only methanol did not inhibit the 7-hydroxylation of coumarin (0.5 to 50 .mu.M) by human liver microsomes. Dioxane and THF, which are structurally related to coumarin, were the most inhibitory solvents examd. Although the rates of coumarin 7-hydroxylation varied enormously among nine samples of human liver microsomes and cDNA-expressed CYP2A6 (Vmax = 179 to 2470 pmol/mg protein/min), the Km for coumarin 7-hydroxylation was fairly const. (ranging from 0.50 to 0.70 .mu.M). The following chems. caused little or no inhibition of CYP2A6 as defined by a Ki > 200 .mu.M: caffeine, chlorzoxazone, cimetidine, dextromethorphan, diazepam, diclofenac, erythromycin, ethynylestradiol, ethynyltestosterone, fluconazole, furafylline, furfural, hexobarbital, itraconazole, mephenytoin, methimazole, metronidazole, naringenin, naringin, nifedipine, norfloxacin, norgestrel, **orphenadrine**, quinidine, papaverine, phenacetin, pyrimethamine, ranitidine, spironolactone, sulfaphenazole, sulfinpyrazone, testosterone, tolbutamide, troleandomycin, and warfarin. In other words, these chems., at a final concn. of 100 .mu.M, failed to inhibit CYP2A6 when the concn. of coumarin was equal to Km (0.50 .mu.M). The following chems. were classified as strong inhibitors of CYP2A6 (defined by Ki < 200 .mu.M): clotrimazole, diethyldithiocarbamate, ellipticine, ketoconazole, 8-methoxypsoralen, 4-methylpyrazole, metyrapone, miconazole, .alpha.-naphthoflavone, nicotine, p-nitrophenol, and tranylcypromine. The potency with which each chem. inhibited the 7-hydroxylation of coumarin was independent of which sample of human liver microsomes was studied. One of the most potent inhibitors of coumarin 7-hydroxylase was 8-methoxypsoralen (**methoxsalen**), which was detd. to be a mechanism-based inhibitor (suicide substrate) of CYP2A6 (kinactivation 0.5 min-1). With the exception of 8-methoxypsoralen, preincubation of human liver microsomes and NADPH with the aforementioned inhibitors did not increase their ability to inhibit CYP2A6. The most potent competitive inhibitor of CYP2A6 was tranylcypromine (Ki = 0.04 .mu.M). Several of the chems. that strongly inhibited CYP2A6, such as ketoconazole and tranylcypromine, are often used with the intention of selectively inhibiting human P 450 enzymes other than CYP2A6.
IT 50-12-4, Mephenytoin 52-01-7, Spironolactone 54-11-5, Nicotine 54-36-4, Metyrapone 56-29-1, Hexobarbital 56-54-2, Quinidine 57-63-6, Ethynylestradiol 57-96-5, Sulfinpyrazone 58-08-2, Caffeine, biological studies 58-14-0, Pyrimethamine 58-22-0, Testosterone 58-74-2, Papaverine 60-56-0, Methimazole 62-44-2, Phenacetin 64-17-5, Ethanol, biological studies 64-77-7, Tolbutamide 67-56-1, Methanol, biological studies 67-63-0, 2-Propanol, biological studies 67-64-1, Acetone, biological studies 67-68-5, DMSO, biological studies 68-12-2, DMF, biological studies 75-05-8, Acetonitrile, biological

studies 81-81-2, Warfarin 83-98-7, **Orphenadrine** 95-25-0, Chlorzoxazone 98-01-1, Furfural, biological studies 100-02-7, p-Nitrophenol, biological studies 109-99-9, Tetrahydrofuran, biological studies 114-07-8, Erythromycin 123-91-1, Dioxane, biological studies 125-71-3, Dextromethorphan 147-84-2, biological studies 155-09-9, Tranylcypromine **298-81-7**, 8-Methoxypsoralen 434-03-7 439-14-5, Diazepam 443-48-1, Metronidazole 480-41-1, Naringenin 519-23-3, Ellipticine 526-08-9, Sulfaphenazole 604-59-1, .alpha.-Naphthoflavone 2751-09-9, Troleandomycin 6533-00-2, Norgestrel 7554-65-6, 4-Methylpyrazole 10236-47-2, Naringin 15307-86-5, Diclofenac 21829-25-4, Nifedipine 22916-47-8, Miconazole 23593-75-1, Clotrimazole 51481-61-9, Cimetidine 65277-42-1, Ketoconazole 66357-35-5, Ranitidine 70458-96-7, Norfloxacin 80288-49-9, Furafylline 84625-61-6, Itraconazole 86386-73-4, Fluconazole
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(coumarin hydroxylase inhibition in human liver microsomes)

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=> d his

     (FILE 'HOME' ENTERED AT 17:15:02 ON 10 APR 2002)

     FILE 'REGISTRY' ENTERED AT 17:15:12 ON 10 APR 2002
                E METHOXSALEN/CN
L1              1 S E3

     FILE 'CAPLUS, USPATFULL' ENTERED AT 17:15:41 ON 10 APR 2002
L2           2642 S L1
L3           2782 S (L2 OR METHOXSALEN?)
L4             52 S L3 AND (NICOTINE OR CYP2A6 OR COTININE OR TOBACCO OR SMOKING)
L5             52 DUP REM L4 (0 DUPLICATES REMOVED)
L6             17 S L5 AND PY<=1996
L7              4 S L4 AND CYP2B6
L8              0 S L5 AND PY<=199
L9             28 S L5 AND PY<=1999
L10           489 S ORPHENADRIN?
L11            80 S L10 AND (NICOTINE OR CYP2A6 OR COTININE OR TOBACCO OR SMOKING
L12            80 DUP REM L11 (0 DUPLICATES REMOVED)
L13            57 S L12 AND PY<=1999
L14            22 S CYP2B6(P)(INHIBITOR OR ANTAGONSIT#) AND (NICOTINE OR CYP2A6 O
L15            19 S L14 AND PY <=1999
L16             0 S CYP2B6(P)(INHIBITOR OR ANTAGONIST#) AND (NICOTINE OR TOBACCO
L17            74 S L10 AND (NICOTINE OR COTININE OR TOBACCO OR SMOKING)
L18            51 S L17 AND PY<=1999
L19            42 S L17 AND PY<=1997

     FILE 'STNGUIDE' ENTERED AT 17:49:59 ON 10 APR 2002

     FILE 'CAPLUS, USPATFULL' ENTERED AT 17:54:34 ON 10 APR 2002
L20             2 S L3 AND ORPHENADRIN?
L21             2 DUP REM L20 (0 DUPLICATES REMOVED)

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FILE 'CAPLUS' ENTERED AT 19:00:30 ON 10 APR 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE 'USPATFULL' ENTERED AT 19:00:30 ON 10 APR 2002

=> s (miconazol? or clotrimazol? or aflatoxin(2a)B or coumarin? or furanocoumarin? or imperatorin? or isopimpinellin? or sphondin? or bergapten? or naringenin? or racumin? or nitropyren? or menadion?) and orphenadrin?
L27 82 (MICONAZOL? OR CLOTRIMAZOL? OR AFLATOXIN(2A) B OR COUMARIN? OR FURANOCOUMARIN? OR IMPERATORIN? OR ISOPIMPINELLIN? OR SPHONDIN? OR BERGAPTEN? OR NARINGENIN? OR RACUMIN? OR NITROPYREN? OR MENAD ION?) AND ORPHENADRIN?

=> dup rem l27
PROCESSING COMPLETED FOR L27
L28 81 DUP REM L27 (1 DUPLICATE REMOVED)

=> s l28 py<=1997
MISSING OPERATOR L28 PY<=1997
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l28 and py<=1997
L29 24 L28 AND PY<=1997

=> d l29 abs ibib kwic 1-24

L29 ANSWER 1 OF 24 CAPLUS COPYRIGHT 2002 ACS
AB Comparison of 7-hydroxylation of **coumarin**, a CYP2A6 substrate, in human and African green and cynomolgus monkey liver microsomes was made by an HPLC assay with UV detection. In human liver microsomes, the Km and Vmax values for the metabolic conversion were 2.1 .mu.M and 0.79 nmol/mg/min, resp. While African green monkey showed Km and Vmax values of 2.7 .mu.M and 0.52 nmol/mg/min, which were similar to human, higher Km and Vmax values were found in cynomolgus monkey. **Coumarin** 7-hydroxylation in human and African green monkey was selectively inhibited by methoxsalen and pilocarpine (CYP2A6 inhibitors) but not by other inhibitors, i.e. .alpha.-naphthoflavone (CYP1A1), **orphenadrine** (CYP2B6), sulfaphenazole (CYP2C9), quinidine (CYP2D6), and ketoconazole (CYP3A4). Immunoinhibition results supported CYP2A6 involvement in human and its homolog in monkey in **coumarin** 7-hydroxylation, as only anti-CYP2A6, but not CYP2B1, CYP2C13, CYP2D6, CYP2E1, or CYP3A antibodies, inhibited this conversion. African green monkey was similar to human in catalytic activity of **coumarin** 7-hydroxylation and response to CYP2A6 inhibitors or antibody inhibition. However, the monkey CYP2A6 is not identical to the human in that Ki values were different, and differences were obsd. with some CYP2A6 inhibitors, such as nicotine and methoxsalen, suggesting that, under some circumstances, studies of nicotine kinetics and drug taking behavior in monkey may not be comparable to human.
ACCESSION NUMBER: 1998:150136 CAPLUS
DOCUMENT NUMBER: 128:164257
TITLE: Comparison of CYP2A6 catalytic on **coumarin** 7-hydroxylation in human and monkey liver microsomes
AUTHOR(S): Li, Yan; Li, Ning Yuan; Sellers, Edward M.

CORPORATE SOURCE: Dep. Pharmacology, Medicine, Psychiatry, Univ. Toronto, Toronto, ON, M5S 1A8, Can.
SOURCE: Eur. J. Drug Metab. Pharmacokinet. (1997), 22(4), 295-304
CODEN: EJDPD2; ISSN: 0378-7966
PUBLISHER: Medecine et Hygiene
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Comparison of CYP2A6 catalytic on **coumarin** 7-hydroxylation in human and monkey liver microsomes

SO Eur. J. Drug Metab. Pharmacokinet. (1997), 22(4), 295-304
CODEN: EJDPD2; ISSN: 0378-7966

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ST cytochrome P450 **coumarin** hydroxylation enzyme kinetics; Michaelis const cytochrome P450 **coumarin** hydroxylation; monkey microsome cytochrome P450 **coumarin** hydroxylation

IT Enzyme kinetics
Michaelis constant
Microsome
Monkey
(comparison of CYP2A6 catalytic on **coumarin** 7-hydroxylation in human and monkey liver microsomes)

IT Monoclonal antibodies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(selective inhibition of **coumarin** 7-hydroxylation by CYP2A6 monoclonal antibody)

IT 9035-51-2, Cytochrome P 450, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(CYP2A6; comparison of CYP2A6 catalytic on **coumarin** 7-hydroxylation in human and monkey liver microsomes)

IT 93-35-6, 7-Hydroxycoumarin
RL: BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(comparison of CYP2A6 catalytic on **coumarin** 7-hydroxylation in human and monkey liver microsomes)

IT 91-64-5, **Coumarin**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(comparison of CYP2A6 catalytic on **coumarin** 7-hydroxylation in human and monkey liver microsomes)
IT 147-84-2, Diethyldithiocarbamic acid, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(inhibition of **coumarin** 7-hydroxylation by)
IT 92-13-7, Pilocarpine 298-81-7, Methoxsalen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(selective inhibition of **coumarin** 7-hydroxylation by)

L29 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2002 ACS
AB The kinetics of pentoxifylline formation from lisofylline in human liver microsomes were studied by using selective inhibitors of cytochrome P 450 isoenzymes, correlation studies with specific isoenzyme activities, and cDNA-expressed human CYP1A2 and 2E1. A biphasic model fitted the data best for the formation of pentoxifylline: Km1 = 0.282 .mu.M, Vmax1 = 0.003 nmol/min/mg protein, Km2 = 158 .mu.M and Vmax2 =0.928 nmol/min/mg. Pentoxifylline formation by the low-Km isoform (200 .mu.M lisofylline) required NADPH, was not inhibited by any isoenzyme-specific P 450 inhibitor, and was inhibited only 10% and 20%, resp., by aminobenzotriazole and N-octamylamine. It was concluded that the low-Km enzyme was not a cytochrome P 450. At 5 .mu.M lisofylline the CYP1A2 inhibitor furafylline inhibited pentoxifylline formation by 58.8%, and the nonspecific CYP2E1 inhibitor diethyldithiocarbamate inhibited pentoxifylline formation by 21.7%. When lisofylline was preincubated with furafylline plus diethyldithiocarbamate, inhibition of pentoxifylline formation was increased 71.4%. Microsomal CYP1A2 activity correlated with pentoxifylline formation. However, CYP2E1 activity did not correlate with pentoxifylline formation. Baculovirus insect cell-expressed human CYP1A2 formed pentoxifylline at 0.987 nmol/min/nmol cytochrome P 450 in the presence of 5 .mu.M lisofylline. CDNA-expressed CYP2E1 did not catalyze formation of pentoxifylline. Diethyldithiocarbamate inhibited pentoxifylline formation by 85.7% with cDNA-expressed CYP1A2. It is concluded that CYP1A2 is the high-affinity enzyme catalyzing pentoxifylline formation from lisofylline.
ACCESSION NUMBER: 1997:808548 CAPLUS
DOCUMENT NUMBER: 128:136087
TITLE: Cytochrome P450 isoenzymes involved in lisofylline metabolism to pentoxifylline in human liver microsomes
AUTHOR(S): Lee, Sun H.; Slattery, John T.
CORPORATE SOURCE: Department of Pharmaceutics, University of Washington, Seattle, WA, 98195-7610, USA
SOURCE: Drug Metab. Dispos. (**1997**), 25(12), 1354-1358
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Drug Metab. Dispos. (**1997**), 25(12), 1354-1358
CODEN: DMDSAI; ISSN: 0090-9556
IT 56-54-2, Quinidine 64-77-7, Tolbutamide 83-98-7, **Orphenadrine** 91-64-5, **Coumarin** 147-84-2, biological studies 526-08-9, Sulfaphenazole 2751-09-9, Troleandomycin 70989-04-7, S-Mephenytoin 80288-49-9, Furafylline
RL: BAC (Biological activity or effector, except adverse); BIOL

(Biological study)
(lisofylline metab. to pentoxifylline in human liver microsome response to)

L29 ANSWER 3 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB RP 73401 is a potent inhibitor of cyclic nucleotide phosphodiesterase type IV. RP 73401 is metabolized by human liver microsomes almost exclusively by trans-hydroxylation of the cyclopentyl group to RPR 113406. Liq. chromatog./mass spectrometry/mass spectrometry anal. of plasma from patients given RP 73401 also revealed a mol. ion and fragmentation consistent with RPR 113406. Thus, the objective was to det. the oxidative enzyme(s) responsible for RP 73401 hydroxylation. Kinetic consts. of RP 113406 formation ranged from 8 to 26 .mu.M and 0.83 to 5.99 nmol/min/mg protein for Km and Vmax, resp. Enzyme activity varied 23-fold among 15 human liver microsome samples and correlated with CYP2A6-catalyzed **coumarin** hydroxylase (r2 = 0.85) and CYP2B6-catalyzed 7-ethoxytrifluoromethylcoumarin O-deethylase (r2 = 0.82) activities. Chem. inhibition studies showed a 63% decrease in RP 73401 hydroxylation by 500 .mu.M **orphenadrine**. **Coumarin** (10 .mu.M), however, did not inhibit RP 73401 hydroxylation. Also, anti-CYP2B1 IgG produced 85% inhibition of RP 73401 hydroxylation, but only a negligible decline in **coumarin** hydroxylase activity. Of the 10 expressed P 450 forms studied, only CYP2B6 catalyzed RP 73401 hydroxylation. Finally, expressed CYP2B6 showed a high affinity (Km = 22.5 .mu.M) for RP 73401 hydroxylation, similar to the human liver microsome studies.

ACCESSION NUMBER: 1997:645668 CAPLUS
DOCUMENT NUMBER: 127:325908
TITLE: Human liver CYP2B6-catalyzed hydroxylation of RP 73401
AUTHOR(S): Stevens, Jeffrey C.; White, Rebecca B.; Hsu, Shih Hsein; Martinet, Michel
CORPORATE SOURCE: Department of Drug Metabolism and Pharmacokinetics, Rhone-Poulenc Rorer, Collegeville, PA, USA
SOURCE: J. Pharmacol. Exp. Ther. (**1997**), 282(3), 1389-1395
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
SO J. Pharmacol. Exp. Ther. (**1997**), 282(3), 1389-1395
CODEN: JPETAB; ISSN: 0022-3565
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expressed CYP2B6 showed a high affinity (Km = 22.5 .mu.M) for RP 73401 hydroxylation, similar to the human liver microsome studies.

L29 ANSWER 4 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB 7-Ethoxy-4-trifluoromethylcoumarin (7-EFC) was examd. as a substrate for cytochrome P 450 (P 450) in microsomes from human livers and expressed in B-lymphoblastoid cells. The O-deethylation of 7-EFC to 7-hydroxy-4-trifluoromethylcoumarin (7-HFC) varied over a liver bank by a factor of 13 (40-507 pmol min-1mg-1 protein). When compared with the ability of the bank of human liver samples to metabolize form-selective substrates of the P 450, 7-HFC formation correlated strongly with the formation of the S-mephenytoin metabolite, nirvanol (r2 = 0.86). .alpha.-Naphthoflavone (ANF), diethyldithiocarbamate (DDC) and chloramphenicol (CAP) inhibited the O-deethylation of 7-EFC by microsomes from human livers by greater than 60%. **Orphenadrine** (ORP), a reported specific CYP2B6 inhibitor, was a less potent inhibitor of 7-HFC formation by microsomes from human liver than DDC or ANF. Using microsomes from B-lymphoblastoid cells expressing specific P450s, CYP2B6 and CYP1A2 were found to produce substantial levels of 7-HFC whereas CYP2E1 and CYP2C19 produced detectable amts. of this metabolite. ORP inhibited expressed CYP2E1 and CYP2B6 mediated 7-HFC formation to a greater extent than the inhibition obsd. for CYP1A2. Methoxychlor and S-mephenytoin inhibited expressed CYP2B6 but not CYP1A2 mediated 7-EFC O-deethylation. Livers with high relative rates of 7-HFC formation displayed biphasic enzyme kinetics with the low Km site (av. Km = 3.3 .mu.M) demonstrating allosteric activation. Five livers with low relative rates of 7-HFC formation also exhibited biphasic kinetics but lacked evidence of an allosteric mechanism being involved in the low Km component (av. Km = 2.4 .mu.M). Furthermore, expressed CYP2B6 and CYP2E1 converted 7-EFC to 7-HFC with allosteric activation indicated, while CYP1A2 mediated metab. of 7-EFC to 7-HFC best fit the classic Michaelis-Menten model. A com. available antibody to rat CYP2B, suggested to be specific for CYP2B6, was found to cross react with all members of the CYP2 family examd. including CYP2C19, which possessed a nearly identical electrophoretic mobility to that of CYP2B6 in the system examd. In total, the evidence presented indicates that multiple P450s are involved in the formation of 7-HFC from 7-EFC, therefore this does not appear to be a useful or a selective probe of CYP2B6 catalytic activity. Furthermore, the specificity of both antibody and chem. inhibitor (ORP) probes previously suggested to be specific for CYP2B6 is also questioned.

ACCESSION NUMBER: 1997:498564 CAPLUS
DOCUMENT NUMBER: 127:187361
TITLE: Examination of purported probes of human CYP2B6
AUTHOR(S): Ekins, Sean; VandenBranden, Mark; Ring, Barbara J.; Wrighton, Steven A.
CORPORATE SOURCE: Department of Drug Disposition, Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, 46285, USA
SOURCE: Pharmacogenetics (**1997**), 7(3), 165-179
CODEN: PHMCEE; ISSN: 0960-314X
PUBLISHER: Chapman & Hall
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Pharmacogenetics (**1997**), 7(3), 165-179
CODEN: PHMCEE; ISSN: 0960-314X

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IT 56-54-2, Quinidine 56-75-7, CAP 83-98-7, ORP 91-64-5, **Coumarin** 147-84-2, DDC, biological studies 526-08-9, Sulphaphenazole 604-59-1, ANF 2751-09-9, TAO 70989-04-7, S-Mephenytoin 80288-49-9, Furafylline
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(examn. of purported probes of human CYP2B6)

L29 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB Nine org. solvents and 47 commonly used P 450 substrates and inhibitors were examd. for their effects on **coumarin** 7-hydroxylase (CYP2A6) activity in human liver microsomes. Of the nine org. solvents examd. (final concn. 1%, vol./vol.), only methanol did not inhibit the 7-hydroxylation of **coumarin** (0.5 to 50 .mu.M) by human liver microsomes. Dioxane and THF, which are structurally related to **coumarin**, were the most inhibitory solvents examd. Although the rates of **coumarin** 7-hydroxylation varied enormously among nine samples of human liver microsomes and cDNA-expressed CYP2A6 (Vmax = 179 to 2470 pmol/mg protein/min), the Km for **coumarin** 7-hydroxylation was fairly const. (ranging from 0.50 to 0.70 .mu.M). The following chems. caused little or no inhibition of CYP2A6 as defined by a Ki > 200 .mu.M: caffeine, chlorzoxazone, cimetidine, dextromethorphan, diazepam, diclofenac, erythromycin, ethynylestradiol, ethynyltestosterone, fluconazole, furafylline, furfural, hexobarbital, itraconazole, mephenytoin, methimazole, metronidazole, **naringenin**, naringin,

nifedipine, norfloxacin, norgestrel, **orphenadrine**, quinidine, papaverine, phenacetin, pyrimethamine, ranitidine, spironolactone, sulfaphenazole, sulfinpyrazone, testosterone, tolbutamide, troleandomycin, and warfarin. In other words, these chems., at a final concn. of 100 .mu.M, failed to inhibit CYP2A6 when the concn. of **coumarin** was equal to Km (0.50 .mu.M). The following chems. were classified as strong inhibitors of CYP2A6 (defined by Ki < 200 .mu.M): **clotrimazole**, diethyldithiocarbamate, ellipticine, ketoconazole, 8-methoxypsoralen, 4-methylpyrazole, metyrapone, **miconazole**, .alpha.-naphthoflavone, nicotine, p-nitrophenol, and tranylcypromine. The potency with which each chem. inhibited the 7-hydroxylation of **coumarin** was independent of which sample of human liver microsomes was studied. One of the most potent inhibitors of **coumarin** 7-hydroxylase was 8-methoxypsoralen (methoxsalen), which was detd. to be a mechanism-based inhibitor (suicide substrate) of CYP2A6 (kinactivation 0.5 min-1). With the exception of 8-methoxypsoralen, preincubation of human liver microsomes and NADPH with the aforementioned inhibitors did not increase their ability to inhibit CYP2A6. The most potent competitive inhibitor of CYP2A6 was tranylcypromine (Ki = 0.04 .mu.M). Several of the chems. that strongly inhibited CYP2A6, such as ketoconazole and tranylcypromine, are often used with the intention of selectively inhibiting human P 450 enzymes other than CYP2A6.

ACCESSION NUMBER: 1997:287113 CAPLUS
DOCUMENT NUMBER: 126:273360
TITLE: Inhibition of **coumarin** 7-hydroxylase activity in human liver microsomes
AUTHOR(S): Draper, Alison J.; Madan, Ajay; Parkinson, Andrew
CORPORATE SOURCE: Dep. Pharmacol., Toxicol., Therapeutics, Cent. Environ. Occupational Health, Univ. Kansas Med. Cent., Kansas City, KS, 66160-7417, USA
SOURCE: Arch. Biochem. Biophys. (**1997**), 341(1), 47-61
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Inhibition of **coumarin** 7-hydroxylase activity in human liver microsomes

SO Arch. Biochem. Biophys. (**1997**), 341(1), 47-61
CODEN: ABBIA4; ISSN: 0003-9861

AB Nine org. solvents and 47 commonly used P 450 substrates and inhibitors were examd. for their effects on **coumarin** 7-hydroxylase (CYP2A6) activity in human liver microsomes. Of the nine org. solvents examd. (final concn. 1%, vol./vol.), only methanol did not inhibit the 7-hydroxylation of **coumarin** (0.5 to 50 .mu.M) by human liver microsomes. Dioxane and THF, which are structurally related to **coumarin**, were the most inhibitory solvents examd. Although the rates of **coumarin** 7-hydroxylation varied enormously among nine samples of human liver microsomes and cDNA-expressed CYP2A6 (Vmax = 179 to 2470 pmol/mg protein/min), the Km for **coumarin** 7-hydroxylation was fairly const. (ranging from 0.50 to 0.70 .mu.M). The following chems. caused little or no inhibition of CYP2A6 as defined by a Ki > 200 .mu.M: caffeine, chlorzoxazone, cimetidine, dextromethorphan, diazepam, diclofenac, erythromycin, ethynylestradiol, ethynyltestosterone, fluconazole, furafylline, furfural, hexobarbital, itraconazole, mephenytoin, methimazole, metronidazole, **naringenin**, naringin, nifedipine, norfloxacin, norgestrel, **orphenadrine**, quinidine, papaverine, phenacetin, pyrimethamine, ranitidine, spironolactone,

sulfaphenazole, sulfinpyrazone, testosterone, tolbutamide, troleandomycin, and warfarin. In other words, these chems., at a final concn. of 100 .mu.M, failed to inhibit CYP2A6 when the concn. of **coumarin** was equal to Km (0.50 .mu.M). The following chems. were classified as strong inhibitors of CYP2A6 (defined by Ki < 200 .mu.M): **clotrimazole**, diethyldithiocarbamate, ellipticine, ketoconazole, 8-methoxypsoralen, 4-methylpyrazole, metyrapone, **miconazole**, .alpha.-naphthoflavone, nicotine, p-nitrophenol, and tranylcypromine. The potency with which each chem. inhibited the 7-hydroxylation of **coumarin** was independent of which sample of human liver microsomes was studied. One of the most potent inhibitors of **coumarin** 7-hydroxylase was 8-methoxypsoralen (methoxsalen), which was detd. to be a mechanism-based inhibitor (suicide substrate) of CYP2A6 (kinactivation 0.5 min-1). With the exception of 8-methoxypsoralen, preincubation of human liver microsomes and NADPH with the aforementioned inhibitors did not increase their ability to inhibit CYP2A6. The most potent competitive inhibitor of CYP2A6 was tranylcypromine (Ki = 0.04 .mu.M). Several of the chems. that strongly inhibited CYP2A6, such as ketoconazole and tranylcypromine, are often used with the intention of selectively inhibiting human P 450 enzymes other than CYP2A6.

ST chem inhibition **coumarin** hydroxylase liver microsome; solvent inhibition **coumarin** hydroxylase liver microsome; cytochrome P 450 substrate **coumarin** hydroxylase

IT Liver
Microsome
Organic solvents
(**coumarin** hydroxylase inhibition in human liver microsomes)

IT 9035-51-2, Cytochrome P 450, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(2A6, substrates and inhibitors; **coumarin** hydroxylase inhibition in human liver microsomes)

IT 50-12-4, Mephenytoin 52-01-7, Spironolactone 54-11-5, Nicotine 54-36-4, Metyrapone 56-29-1, Hexobarbital 56-54-2, Quinidine 57-63-6, Ethynylestradiol 57-96-5, Sulfinpyrazone 58-08-2, Caffeine, biological studies 58-14-0, Pyrimethamine 58-22-0, Testosterone 58-74-2, Papaverine 60-56-0, Methimazole 62-44-2, Phenacetin 64-17-5, Ethanol, biological studies 64-77-7, Tolbutamide 67-56-1, Methanol, biological studies 67-63-0, 2-Propanol, biological studies 67-64-1, Acetone, biological studies 67-68-5, DMSO, biological studies 68-12-2, DMF, biological studies 75-05-8, Acetonitrile, biological studies 81-81-2, Warfarin 83-98-7, **Orphenadrine** 95-25-0, Chlorzoxazone 98-01-1, Furfural, biological studies 100-02-7, p-Nitrophenol, biological studies 109-99-9, Tetrahydrofuran, biological studies 114-07-8, Erythromycin 123-91-1, Dioxane, biological studies 125-71-3, Dextromethorphan 147-84-2, biological studies 155-09-9, Tranylcypromine 298-81-7, 8-Methoxypsoralen 434-03-7 439-14-5, Diazepam 443-48-1, Metronidazole 480-41-1, **Naringenin** 519-23-3, Ellipticine 526-08-9, Sulfaphenazole 604-59-1, .alpha.-Naphthoflavone 2751-09-9, Troleandomycin 6533-00-2, Norgestrel 7554-65-6, 4-Methylpyrazole 10236-47-2, Naringin 15307-86-5, Diclofenac 21829-25-4, Nifedipine 22916-47-8, **Miconazole** 23593-75-1, **Clotrimazole** 51481-61-9, Cimetidine 65277-42-1, Ketoconazole 66357-35-5, Ranitidine 70458-96-7, Norfloxacin 80288-49-9, Furafylline 84625-61-6, Itraconazole 86386-73-4, Fluconazole
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**coumarin** hydroxylase inhibition in human liver microsomes)

IT 39401-02-0, **Coumarin** 7-hydroxylase
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**coumarin** hydroxylase inhibition in human liver microsomes)

L29 ANSWER 6 OF 24 CAPLUS COPYRIGHT 2002 ACS
AB In vitro methods were used to identify the cytochrome P 450 (CYP) enzyme(s) involved in S-mephenytoin N-demethylation. S-mephenytoin (200 .mu.M) was incubated with human liver microsomes, and nirvanol formation was quantitated by reversed-phase HPLC. Mephenytoin N-demethylase activity in a panel of human liver microsomes ranged 35-fold from 9 to 319 pmol/min protein and correlated strongly with microsomal CYP2B6 activity (r = 0.91). Addnl. correlation were found with microsomal CYP2A6 and CYP3A4 activity (r = 0.88 and 0.74, resp.). Microsomes prepd. from human .beta.-lymphoblastoid cells transformed with individual P 450 cDNAs were assayed for S-mephenytoin N-demethylase activity. Of 11 P 450 isoforms (P450s 1A1, 1A2, 2A6, 2B6, 2E1, 2D6, 2C8, 2C9, 3A4, and 3A5) tested, only CYP2B6 catalyzed the N-demethylation of S-mephenytoin with an apparent Km of 564 .mu.M. Expts. with P 450 form-selective chem. inhibitors, competitive substrates, and anti-P 450 antibodies were also performed. Troleandomycin, a mechanism-based CYP3A selective inhibitor, and **coumarin**, a substrate for CYP2A6 and therefore a potential competitive inhibitor, failed to inhibit human liver microsomal S-mephenytoin N-demethylation. In contrast, **orphenadrine**, an inhibitor of CYP2B forms, produced at 51.OMEGA.4% decrease in S-mephenytoin N-demethylase activity in human liver microsomes and a 45% decrease in recombinant microsomes expressing CYP2B6. Also, both CYP2B6-marker 7-ethoxytrifluoromethylcoumarin O-deethylase and S-mephenytoin N-demethylase activities were inhibited by .apprx.65% by 5 mg anti-CYP2B1 IgG/mg microsomal protein. Finally, polyclonal antibody inhibitory to CYP3A1 failed to inhibit S-mephenytoin N-demethylase activity. Taken together, these studies indicate that the N-demethylation of S-mephenytoin by human liver microsomes is catalyzed primarily by CYP2B6.

ACCESSION NUMBER: 1996:589147 CAPLUS
DOCUMENT NUMBER: 125:264890
TITLE: Catalytic role of cytochrome P4502B6 in the N-demethylation of S-mephenytoin
AUTHOR(S): Heyn, Heleen; White, Rebecca B.; Stevens, Jeffrey C.
CORPORATE SOURCE: Dep. Drug Metab. Pharmacokinetics, Rhone-Poulenc Rorer Res. Development, Collegeville, PA, 19426-0107, USA
SOURCE: Drug Metab. Dispos. (**1996**), 24(9), 948-954
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Drug Metab. Dispos. (**1996**), 24(9), 948-954
CODEN: DMDSAI; ISSN: 0090-9556
AB In vitro methods were used to identify the cytochrome P 450 (CYP) enzyme(s) involved in S-mephenytoin N-demethylation. S-mephenytoin (200 .mu.M) was incubated with human liver microsomes, and nirvanol formation was quantitated by reversed-phase HPLC. Mephenytoin N-demethylase activity in a panel of human liver microsomes ranged 35-fold from 9 to 319 pmol/min protein and correlated strongly with microsomal CYP2B6 activity (r = 0.91). Addnl. correlation were found with microsomal CYP2A6 and CYP3A4 activity (r = 0.88 and 0.74, resp.). Microsomes prepd. from human .beta.-lymphoblastoid cells transformed with individual P 450 cDNAs were assayed for S-mephenytoin N-demethylase activity. Of 11 P 450 isoforms (P450s 1A1, 1A2, 2A6, 2B6, 2E1, 2D6, 2C8, 2C9, 3A4, and 3A5) tested, only

CYP2B6 catalyzed the N-demethylation of S-mephenytoin with an apparent Km of 564 .mu.M. Expts. with P 450 form-selective chem. inhibitors, competitive substrates, and anti-P 450 antibodies were also performed. Troleandomycin, a mechanism-based CYP3A selective inhibitor, and **coumarin**, a substrate for CYP2A6 and therefore a potential competitive inhibitor, failed to inhibit human liver microsomal S-mephenytoin N-demethylation. In contrast, **orphenadrine**, an inhibitor of CYP2B forms, produced at 51.OMEGA.4% decrease in S-mephenytoin N-demethylase activity in human liver microsomes and a 45% decrease in recombinant microsomes expressing CYP2B6. Also, both CYP2B6-marker 7-ethoxytrifluoromethylcoumarin O-deethylase and S-mephenytoin N-demethylase activities were inhibited by .apprx.65% by 5 mg anti-CYP2B1 IgG/mg microsomal protein. Finally, polyclonal antibody inhibitory to CYP3A1 failed to inhibit S-mephenytoin N-demethylase activity. Taken together, these studies indicate that the N-demethylation of S-mephenytoin by human liver microsomes is catalyzed primarily by CYP2B6.

L29 ANSWER 7 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB The volatile anesthetic sevoflurane is degraded by strong gases in the carbon dioxide absorbent in clin. anesthesia machines to fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether (FDVE, also called "Compd. A"). FDVE is nephrotoxic in rats, where it is extensively biotransformed. Patients undergoing sevoflurane anesthesia have been exposed to low inhaled concns. of FDVE. Although sevoflurane renal toxicity under conditions of FDVE formation has not been reported, there is still considerable concern about FDVE metab. in humans and the potential for FDVE nephrotoxicity. Sevoflurane undergoes P 450-catalyzed liver microsomal defluorination. We tested the hypothesis that FDVE also undergoes human liver microsomal defluorination. Defluorination occurred both in the absence and presence of NADPH; rates of total and NADPH-dependent fluoride formation were 1.6 and 1 nmol.cntdot.min-1.cntdot.mg-1 protein (mean), resp. in four human livers. Enzymic defluorination was linear with respect to time, protein concn., and was saturable with respect to substrate concn. NADPH-dependent, but not NADPH-independent, FDVE defluorination was partially inhibited by **coumarin**, **orphenadrine**, diethyldithiocarbamate, and 4-methylpyrazole. Microsomes contg. cDNA-expressed human P 4502E1 exhibited substantial catalytic activity toward FDVE defluorination. Microsomal FDVE defluorination was significantly diminished in the presence of the parent anesthetic, sevoflurane, from 1.3 to 0.6 nmol.cntdot.min-1.cntdot.mg-1. These results show that FDVE undergoes both P 450-catalyzed and nonenzymic defluorination by human liver microsomes. P 4502E1 is implicated in the enzymic defluorination. Nonenzymic defluorination may result from FDVE addn. to protein thiols. Enzymic and/or nonenzymic defluorination may be etiol. factors in FDVE nephrotoxicity in rats. In contrast, P 450-dependent FDVE defluorination may be of less clin. consequence in humans, because it is inhibited by the parent anesthetic, sevoflurane.

ACCESSION NUMBER: 1996:364854 CAPLUS
DOCUMENT NUMBER: 125:48297
TITLE: P450-dependent and nonenzymic human liver microsomal defluorination of fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether (compound A), a sevoflurane degradation product
AUTHOR(S): Kharasch, Evan D.; Hankins, Douglas C.
CORPORATE SOURCE: Dep. Anesthesiology and Medicinal Chem., Univ. Washington, Seattle, WA, 98195, USA

SOURCE: Drug Metab. Dispos. (1996), 24(6), 649-654
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Drug Metab. Dispos. (1996), 24(6), 649-654
CODEN: DMDSAI; ISSN: 0090-9556
AB The volatile anesthetic sevoflurane is degraded by strong gases in the carbon dioxide absorbent in clin. anesthesia machines to fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether (FDVE, also called "Compd. A"). FDVE is nephrotoxic in rats, where it is extensively biotransformed. Patients undergoing sevoflurane anesthesia have been exposed to low inhaled concns. of FDVE. Although sevoflurane renal toxicity under conditions of FDVE formation has not been reported, there is still considerable concern about FDVE metab. in humans and the potential for FDVE nephrotoxicity. Sevoflurane undergoes P 450-catalyzed liver microsomal defluorination. We tested the hypothesis that FDVE also undergoes human liver microsomal defluorination. Defluorination occurred both in the absence and presence of NADPH; rates of total and NADPH-dependent fluoride formation were 1.6 and 1 nmol.cntdot.min-1.cntdot.mg-1 protein (mean), resp. in four human livers. Enzymic defluorination was linear with respect to time, protein concn., and was saturable with respect to substrate concn. NADPH-dependent, but not NADPH-independent, FDVE defluorination was partially inhibited by **coumarin**, **orphenadrine**, diethyldithiocarbamate, and 4-methylpyrazole. Microsomes contg. cDNA-expressed human P 4502E1 exhibited substantial catalytic activity toward FDVE defluorination. Microsomal FDVE defluorination was significantly diminished in the presence of the parent anesthetic, sevoflurane, from 1.3 to 0.6 nmol.cntdot.min-1.cntdot.mg-1. These results show that FDVE undergoes both P 450-catalyzed and nonenzymic defluorination by human liver microsomes. P 4502E1 is implicated in the enzymic defluorination. Nonenzymic defluorination may result from FDVE addn. to protein thiols. Enzymic and/or nonenzymic defluorination may be etiol. factors in FDVE nephrotoxicity in rats. In contrast, P 450-dependent FDVE defluorination may be of less clin. consequence in humans, because it is inhibited by the parent anesthetic, sevoflurane.

L29 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2002 ACS
AB Principal components anal. (PCA) of standardized RF values of 443 drugs and their metabolites present in urine and blood samples chromatographed with four sheet systems provided a two-component model accounting for 70.8% of the total variance. The "scores" plot enabled either identification, or restriction of the range of inquiry to few candidates. This simple, cheap and fast anal. method is of vital importance in the identification of an unknown drug in cases of overdose intoxication or poisoning.

ACCESSION NUMBER: 1994:644897 CAPLUS
DOCUMENT NUMBER: 121:244897
TITLE: Qualitative organic analysis. Part 3. Identification of drugs and their metabolites by PCA of standardized TLC data
AUTHOR(S): Romano, Guido; Caruso, Giuseppe; Musumarra, Giuseppe; Pavone, Didier; Cruciani, Gabriele
CORPORATE SOURCE: Istituto di Medicina Legale e delle Assicurazioni, Univ. Catania, Catania, 95124, Italy
SOURCE: J. Planar Chromatogr.--Mod. TLC (1994), 7(3), 233-41
CODEN: JPCTE5; ISSN: 0933-4173

DOCUMENT TYPE: Journal
LANGUAGE: English
SO J. Planar Chromatogr.--Mod. TLC (1994), 7(3), 233-41
CODEN: JPCTE5; ISSN: 0933-4173

IT 50-36-2, Cocaine 50-37-3, Lysergide 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-52-2, Thioridazine 50-53-3, analysis 50-55-5, Reserpine 50-60-2, Phentolamine 51-06-9, Procainamide 51-34-3, Scopolamine 51-55-8, Atropine, analysis 51-68-3, Meclofenoxate 52-53-9, Verapamil 52-53-9D, Verapamil, metabolites 52-86-8, Haloperidol 54-03-5, Hexobendine 54-05-7, Chloroquine 54-11-5, Nicotine 54-31-9, Furosemide 54-32-0, Moxisylyte 54-85-3, Isoniazid 55-65-2, Guanethidine 56-54-2, Quinidine 57-24-9, Strychnine 57-27-2, Morphine, analysis 57-42-1, Meperidine 57-96-5, Sulfinpyrazone 58-08-2, Caffeine, analysis 58-15-1, Aminopyrine 58-25-3, Chlordiazepoxide 58-32-2, Dipyridamole 58-38-8, Prochlorperazine 58-39-9, Perphenazine 58-40-2, Promazine 58-55-9, Theophylline, analysis 58-73-1, Diphenhydramine 58-74-2, Papaverine 59-26-7, Nikethamide 59-46-1, Procaine 59-87-0, Nitrofurazone 60-80-0, Antipyrine 60-87-7, Promethazine 60-99-1, Methotrimeprazine 61-00-7, Acepromazine 62-44-2, Phenacetin 62-67-9, Nalorphine 64-86-8 64-95-9, Adiphenine 68-88-2, Hydroxizine 68-89-3, Dipyrone 69-23-8, Fluphenazine 69-43-2, Prenylamine lactate 72-44-6, Methaqualone 72-69-5, Nortriptyline 73-09-6, Etozolin 74-55-5, Ethambutol 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-58-4, Ethylmorphine 76-99-3, Methadone 76-99-3D, Methadone, metabolites 77-07-6, Levorphanol 77-10-1, Phencyclidine 77-15-6, Ethoheptazine 77-19-0, Dicyclomine 77-37-2, Procyclidine 77-39-4, Cycrimine 77-67-8, Ethosuximide 80-77-3, Chlormezanone 82-88-2 82-92-8, Cyclizine 82-98-4, Piperidolate 83-07-8 83-15-8 83-67-0, Theobromine 83-98-7, **Orphenadrine** 84-22-0, Tetrahydrozoline 84-36-6, Syrosingopine 84-55-9, Viquidil 86-12-4 86-21-5, Pheniramine 86-22-6, Brompheniramine 86-42-0, Amodiaquin 86-75-9, Benzoxiquine 90-39-1, Sparteine 90-54-0, Etafenone 91-79-2, Thenyldiamine 91-81-6, Tripelenamine 91-84-9 92-12-6, Phenyltoloxamine 92-13-7, Pilocarpine 93-30-1, Methoxyphenamine 96-88-8, Mepivacaine 97-77-8, Disulfiram 99-43-4, Benoxinate 100-92-5, Mephentermine 101-40-6, Propylhexedrine 102-45-4, Cyclopentamine 113-42-8, Methylergonovine 113-45-1, Methylphenidate 113-53-1, Dothiepin 113-59-7, Chlorprothixene 113-92-8, Chlorpheniramine maleate 114-86-3, Phenformin 117-89-5, Trifluoperazine 120-29-6, Tropine 125-28-0, Dihydrocodeine 126-27-2, Oxethazaine 127-35-5, Phenazocine 128-62-1, Noscapine 130-26-7, Iodochlorhydroxyquin 130-95-0, Quinine 134-49-6, Phenmetrazine 137-58-6, Lidocaine 138-56-7, Trimethobenzamide 144-11-6, Trihexyphenidyl 146-22-5 146-48-5, Yohimbine 146-54-3, Triflupromazine 152-02-3, Levallorphan 156-08-1, Benzphetamine 298-46-4, Carbamazepine 298-57-7, Cinnarizine 299-42-3 300-62-9, Amphetamine 303-49-1, Clomipramine 303-49-1D, Clomipramine, metabolites 303-53-7, Cyclobenzaprine 309-29-5, Doxapram 314-35-2, Etamiphyllin 317-34-0, Aminophylline 318-23-0, Imolamine 357-57-3, Brucine 359-83-1, Pentazocine 361-37-5, Methysergide 364-62-5, Metoclopramide 372-66-7, Heptaminol 395-28-8, Isoxsuprine 437-38-7, Fentanyl 438-60-8, Protriptyline 439-14-5, Diazepam 443-48-1, Metronidazole 458-24-2, Fenfluramine 465-65-6, Naloxone 466-99-9, Hydromorphone 468-61-1, Oxeladin 469-21-6 469-62-5, Propoxyphene 479-92-5, Propyphenazone 482-15-5, Isothipendyl 483-04-5, Ajmalicine 493-92-5, Prolintane 501-68-8, Beclamide 510-53-2, Racemethorphan 511-12-6, Dihydroergotamine 511-45-5, Pridinol 512-15-2,

Cyclopentolate 514-65-8, Biperiden 519-09-5, Benzoylecgonine 519-98-2 523-87-5, Dimenhydrinate 524-81-2, Mebhydrolin 525-66-6, Propranolol 526-36-3, Xylometazoline 537-26-8, Tropacocaine 537-46-2, Methamphetamine 539-15-1, Hordenine 548-73-2, Droperidol 553-06-0, N-(1,2-Diphenylethyl)nicotinamide 561-27-3, Diacetylmorphine 604-51-3, Deptropine 604-75-1 633-47-6, Cropropamide 634-03-7, Phendimetrazine 642-72-8, Benzydamine 738-70-5, Trimethoprim 739-71-9, Trimipramine 749-13-3, Trifluoperidol 768-94-5, Amantadine 791-35-5, Chlophedianol 804-10-4, Chromonar 835-31-4, Naphazoline 841-77-0, Norcyclizine 846-49-1, Lorazepam 846-50-4, Temazepam 848-75-9, Lormetazepam 852-42-6, Guaiapate 894-76-8, 7-Aminodesmethylflunitrazepam 911-45-5, Clomiphene 915-30-0, Diphenoxylate 952-54-5, Morphazinamide 959-14-8, Oxolamine 982-24-1, Clopenthixol 1028-33-7, Pentifylline 1088-11-5, Desmethyldiazepam 1092-46-2, Ketocaine 1098-97-1, Pyritinol 1165-48-6, Dimefline 1222-57-7, Zolimidine 1420-55-9, Thiethylperazine 1421-14-3, Propanidid 1435-55-8, Hydroquinidine 1491-59-4, Oxymetazoline 1617-90-9, Vincamine 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 1668-19-5, Doxepin 1672-58-8 1812-30-2, Bromazepam 1882-26-4, Pyridinolcarbamate 1893-33-0, Pipamperone 1951-25-3, Amiodarone 1977-10-2, Loxapine 2016-63-9, Bamifylline 2058-52-8, Clothiapine 2062-78-4, Pimozide 2167-85-3, Pipazethate 2180-92-9, Bupivacaine 2470-73-7, Dixyrazine 2558-30-7, Desmethylflunitrazepam 2609-46-3, Amiloride 2622-26-6, Pericyazine 2784-73-8, 6-Monoacetylmorphine 2886-65-9, N-1-Desalkylflurazepam 2894-67-9, Delorazepam 2898-12-6, Medazepam 2955-38-6, Prazepam 3099-52-3, Nicametate 3572-43-8, Bromhexine 3605-01-4, Piribedil 3625-06-7, Mebeverine 3703-76-2, Cloperastine 3703-79-5, Bamethan 3737-09-5, Disopyramide 3820-67-5, Glafenine 3930-20-9, Sotalol 4093-35-0, Bromopride
RL: ANT (Analyte); ANST (Analytical study)
(identification of drugs and metabolites in blood and urine by principal components anal. of standardized thin-layer chromatog. data)

IT 4171-13-5, Valnoctamide 4205-90-7, Clonidine 4360-12-7, Ajmaline 4498-32-2, Dibenzepin 4551-59-1, Fenalamide 4936-47-4, Nifuratel 4945-47-5, Bamipine 4969-02-2, Methixene 5003-48-5, Benorylate 5036-02-2, Tetramisole 5053-06-5, Fenspiride 5118-29-6, Melitracen 5169-78-8, Tipepidine 5633-20-5, Oxybutynin 5636-83-9, Dimethindene 5638-76-6, Betahistine 5696-09-3, Proxazole 5741-22-0, Moprolol 5868-05-3, Niceritrol 6168-76-9, Crotethamide 6452-71-7, Oxprenolol 6493-05-6, Pentoxifylline 6506-37-2, Nimorazole 6621-47-2, Perhexiline 6703-27-1, Acetylcodeine 6740-88-1, Ketamine 6808-72-6, Glaziovine 7262-75-1, Lefetamine 7456-24-8, Fonazine 10236-81-4, Prifinium 10238-21-8, Glibenclamide 10262-69-8, Maprotiline 10402-90-1, Eprazinone 10418-03-8, Stanozolol 10457-90-6, Bromperidol 10539-19-2, Moxaverine 11032-41-0, Dihydroergotoxine 12712-75-3, Succiphylline 13042-18-7, Fendiline 13495-09-5, Piminodine 13523-86-9, Pindolol 13655-52-2, Alprenolol 13669-70-0, Nefopam 14007-64-8, Butethamate 14504-73-5, Tritoqualine 14611-51-9, Selegiline 14860-49-2, Clobutinol 15301-69-6, Flavoxate 15421-84-8, Trapidil 15500-66-0, Pancuronium 15574-96-6, Pizotyline 15676-16-1, Sulpiride 15686-51-8, Clemastine 15687-41-9, Oxyfedrine 16590-41-3, Naltrexone 16662-47-8, Gallopamil 16846-24-5, Josamycin 17449-96-6, Clofezone 17479-19-5, Dihydroergocristine 17617-23-1, Flurazepam 17692-31-8, Dropropizine 17692-51-2, Metergoline 17854-59-0, Mepixanthone 18016-80-3, Lisuride 18046-21-4, Fentiazac 18053-31-1, Fominoben 18109-80-3, Butamirate 18471-20-0, Ditazol 18559-94-9, Albuterol 18683-91-5, Ambroxol 19216-56-9, Prazosin 19794-93-5, Trazodone 20448-86-6, Bornaprine 20971-53-3, N-1-

Hydroxyethylflurazepam 21363-18-8, Viminol 21829-25-4, Nifedipine 21888-98-2, Dexetimide 21946-79-2, Tenitramine 22131-35-7, Butalamine 22232-71-9, Mazindol 22316-47-8, Clobazam 22916-47-8, **Miconazole** 22950-29-4, Dimethophrine 23047-25-8, Lofepramine 23602-78-0, Benfluorex 23779-99-9, Floctafenine 23887-31-2, Clorazepate 23887-41-4, Cinepazet 23887-46-9, Cinepazide 24219-97-4, Mianserin 24526-64-5, Nomifensine 25146-18-3, Febutol 25614-03-3, Bromocriptine 25905-77-5, Minaprine 26095-59-0, Otilonium bromide 26652-09-5, Ritodrine 26807-65-8, Indapamide 26839-75-8, Timolol 27223-35-4, Ketazolam 27367-90-4, Niaprazine 27848-84-6, Nicergoline 28797-61-7, Pirenzepine 28911-01-5, Triazolam 28981-97-7, Alprazolam 29094-61-9, Glipizide 29122-68-7, Atenolol 29216-28-2, Mequitazine 29218-27-7, Toloxatone 29769-70-8, Fenpyramine 29975-16-4, Estazolam 30418-38-3, Tretoquinol 31329-57-4, Nafronyl 31431-39-7, Mebendazole 31828-71-4, Mexiletine 31842-01-0, Indoprofen 31848-01-8, Morclofone 32665-36-4, Eprozinol 32828-81-2, Picotamide 33342-05-1, Gliquidone 33671-46-4, Clotiazepam 34084-50-9, 7-Aminoflunitrazepam 34161-24-5, Fipexide 34580-13-7, Ketotifen 34661-75-1, Urapidil 34758-83-3, Zipeprol 34758-83-3D, Zipeprol, metabolites 35080-11-6, Prajmaline 35619-65-9, Trithiozine 35941-65-2, Butriptyline 36104-80-0, Camazepam 36309-01-0, Dimemorfan 36322-90-4, Piroxicam 36653-54-0, Fazadinium 36735-22-5, Quazepam 36894-69-6, Labetolol 37350-58-6, Metoprolol 37517-30-9, Acebutolol 38304-91-5, Minoxidil 38363-40-5, Penbutolol 39133-31-8, Trimebutine 39516-21-7, Thiopropamine 39562-70-4, Nitrendipine 40054-69-1, Etizolam 40762-15-0, Doxefazepam 42200-33-9, Nadolol 42399-41-7, Diltiazem 46817-91-8, Viloxazine 47562-08-3, Lorajmine 50264-69-2, Lonidamine 50679-08-8, Terfenadine 51012-32-9, Tiapride 51481-61-9, Cimetidine 52463-83-9, Pinazepam 52468-60-7, Flunarizine 52485-79-7, Buprenorphine 52942-31-1, Etoperidone 53179-11-6, Loperamide 53583-79-2, Sultopride 53643-48-4, Vindesine 53716-44-2, Rociverine 54063-53-5, Propafenone 54063-54-6, Reproterol 54739-18-3, Fluvoxamine 54767-75-8, Suloctidil 54910-89-3, Fluoxetine 54946-52-0, Methylenedioxymethamphetamine 55142-85-3, Ticlopidine 55294-15-0, Muzolimine 55837-25-7, Buflomedil 55837-27-9, Piretanide 55905-53-8, Clebopride 55985-32-5, Nicardipine 57132-53-3, Proglumetacin 57574-09-1, Amineptine 57801-81-7, Brotizolam 57808-66-9, Domperidone 59338-93-1, Alizapride 59804-37-4, Tenoxicam 59995-65-2, Pinaverium 60607-34-3, Oxatomide 60607-68-3, Indenolol 61869-07-6, Domiodol 62973-76-6, Azanidazole 63590-64-7, Terazosin 64241-34-5, Cadralazine 65277-42-1, Ketoconazole 66085-59-4, Nimodipine 66195-31-1, Ibopamine 66357-35-5, Ranitidine 66644-81-3, Veralipride 66722-44-9, Bisoprolol 68844-77-9, Astemizole 73590-58-6, Omeprazole 74050-98-9, Ketanserin 74191-85-8, Doxazosin 76963-41-2, Nizatidine 78755-81-4, Flumazenil 82626-48-0, Zolpidem 85441-61-8, Quinapril 88644-76-2

RL: ANT (Analyte); ANST (Analytical study)
(identification of drugs and metabolites in blood and urine by principal components anal. of standardized thin-layer chromatog. data)

L29 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB A controlled-release transdermal pharmaceutical contg. therapeutic agents in a poly(vinyl alc.) (I) cryogel is disclosed. A slurry of 11.0 mg ciprofloxacin.HCl (II) and 200 mg 10% I was warmed to 50-60.degree. to obtain a clear homogeneous soln. The soln. was then placed in a mold and subjected to 6 freeze-thaw cycles to give a white opaque elastomeric cryogel having 15mm diam. and 0.5mm thickness. The release of II from the gel in 0.9% NaCl was 74% in th 1st 4 hs and it was const. in the subsequent 5-24 hs.

ACCESSION NUMBER: 1994:200438 CAPLUS
DOCUMENT NUMBER: 120:200438
TITLE: Controlled-release transdermal pharmaceuticals containing cryogels
INVENTOR(S): Wood, Louis L.; Calton, Gary J.
PATENT ASSIGNEE(S): SRCHEM Inc., USA
SOURCE: U.S., 15 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5260066	A	19931109	US 1992-821627	19920116 <--
US 5288503	A	19940222	US 1992-899369	19920616 <--

PRIORITY APPLN. INFO.: US 1992-821627 19920116
PI US 5260066 A **19931109**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5260066	A	19931109	US 1992-821627	19920116 <--
US 5288503	A	19940222	US 1992-899369	19920616 <--

IT 50-00-0, Formaldehyde, biological studies 50-02-2, Dexamethasone 50-06-6, biological studies 50-07-7, Mitomycin C 50-18-0, Cytoxan 50-23-7, Hydrocortisone 50-24-8, Prednisolone 50-48-6, Amitriptyline 50-49-7, Imipramine 50-52-2, Thioridazine 50-53-3, Chlorpromazine, biological studies 50-56-6, Oxytocin, biological studies 50-76-0, Actinomycin D 50-78-2 50-81-7, Vitamin C, biological studies 51-05-8, Procaine hydrochloride 51-21-8, 5-Fluorouracil 51-34-3, Scopolamine 51-41-2, Levarterenol 51-43-4, Epinephrine 51-48-9, Thyroxine, biological studies 51-64-9, Dextroamphetamine 51-77-4, Gefarnate 52-53-9, Verapamil 52-86-8, Haloperidol 53-03-2, Prednisone 53-06-5, Cortisone 54-31-9, Furosemide 54-42-2, Idoxuridine 54-85-3, Isoniazide 54-91-1, Pipobroman 55-63-0 56-40-6, Glycine, biological studies 56-41-7, Alanine, biological studies 56-45-1, Serine, biological studies 56-54-2, Quinidine 56-75-7, Chloramphenicol 56-84-8, Aspartic acid, biological studies 56-85-9, Glutamine, biological studies 56-86-0, Glutamic acid, biological studies 56-87-1, Lysine, biological studies 57-27-2, Morphine, biological studies 57-41-0, Phenytoin 57-42-1, Meperidine 57-66-9, Probenecid 57-92-1, Streptomycin, biological studies 58-08-2, biological studies 58-14-0, Pyrimethamine 58-32-2, Dipyridamole 58-40-2, Promazine 58-54-8, Ethacrynic acid 58-55-9, Theophylline, biological studies 58-73-1, Diphenhydramine 58-74-2, Papaverine 58-93-5 59-01-8, Kanamycin 59-05-2, Methotrexate 59-33-6 59-46-1, Procaine 59-87-0 59-92-7, Levodopa, biological studies 60-54-8, Tetracycline 61-25-6, Papaverine hydrochloride 61-32-5, Methicillin 61-33-6, preparation 61-72-3, Cloxacillin 61-90-5, L-Leucine, biological studies 62-31-7, Dopamine hydrochloride 62-97-5, Diphemanil 63-68-3, Methionine, biological studies 63-91-2, Phenylalanine, biological studies 64-17-5, Ethanol, biological studies 65-49-6 66-79-5, Oxacillin 67-63-0, Isopropanol, biological studies 68-88-2, Hydroxyzine 69-23-8, Fluphenazine 69-43-2, Prenylamine lactate 69-53-4, Ampicillin 69-72-7, biological studies 70-00-8, Trifluridine 70-30-4, Hexachlorophene 71-00-1, Histidine, biological studies 72-19-5, Threonine, biological studies 72-44-6, Methaqualone 72-69-5 73-22-3, Tryptophan, biological studies 73-32-5, Isoleucine, biological

studies 73-48-3 74-79-3, Arginine, biological studies 76-99-3, Methadone 77-07-6, Levorphanol 77-19-0, Dicyclomine 77-21-4, Glutethimide 78-11-5, Pentaerythritol tetranitrate 79-57-2, Oxytetracycline 81-23-2, Dehydrocholic acid 83-88-5, Vitamin G, biological studies 83-98-7, **Orphenadrine** 85-79-0, Dibucaine 86-21-5, Pheniramine 86-22-6, Brompheniramine 87-08-1, Penicillin V 87-33-2, Isosorbide dinitrate 90-82-4, Pseudoephedrine 91-81-6, Tripelennamine 94-09-7, Benzocaine 95-27-2, Dimazole 100-92-5, Mephentermine 101-31-5, Hyoscyamine 108-46-3, 1,3-Benzenediol, biological studies 112-38-9, Undecylenic acid 113-15-5, Ergotamine 113-92-8 114-07-8, Erythromycin 115-38-8, Methylphenobarbital 118-23-0, Bromodiphenhydramine 118-42-3, Hydroxychloroquine 121-54-0 122-09-8, Phentermine 122-11-2, Sulfadimethoxine 125-29-1, Hydrocodone 125-71-3, Dextromethorphan 126-07-8, Griseofulvin 127-33-3, Demeclocycline 127-69-5, Sulfisoxazole 128-62-1, Noscapine 129-16-8, Mercurochrome 132-17-2 133-15-3 133-67-5, Trichlormethiazide 136-96-9 137-58-6, Lidocaine 144-80-9, Sulfacetamide 144-82-1, Sulfamethizole 147-24-0, Diphenhydramine hydrochloride 147-52-4, Nafcillin 147-85-3, Proline, biological studies 148-82-3, Melphalan 151-21-3, Sodium lauryl sulfate, biological studies 153-61-7, Cephalothin 154-21-2 298-57-7, Cinnarizine 300-62-9, Amphetamine 302-17-0, Chloral hydrate 302-79-4, Retinoic acid 303-81-1, Novobiocin 303-98-0 318-98-9 359-83-1, Pentazocine 361-37-5, Methysergide 389-08-2, Nalidixic acid 395-28-8, Isoxsuprine 437-38-7, Fentanyl 439-14-5, Diazepam 447-41-6 466-99-9, Hydromorphone 469-62-5, Propoxyphene 471-53-4, Glycyrrhetic acid 479-18-5, Diprophylline 486-12-4, Triprolidine 496-67-3, Bromovalerylurea 514-65-8, Biperiden 515-64-0, Sulfisomidine 525-66-6, Propranolol 554-13-2, Lithium carbonate 562-10-7 564-25-0, Doxycycline 569-65-3, Meclizine 634-03-7, Phendimetrazine 645-05-6, HMM 668-94-0 671-16-9, Procarbazine 777-11-7, Haloprogin 804-10-4 807-38-5, Fluocinolone 835-31-4, Naphazoline 914-00-1, Methacycline 940-69-2, Vitamin N 1018-71-9, Pyrrolnitrin 1066-17-7, Colistin 1070-11-7 1115-84-0, Vitamin U 1172-18-5, Flurazepam hydrochloride 1319-77-3, Cresol 1319-82-0, Aminocaproic acid 1333-08-0, Ethyl aminobenzoate 1333-73-9, Sodium borate 1340-08-5, Vitamin P 1394-02-1, Trichomycin 1397-89-3, Amphotericin B 1400-61-9, Nystatin 1403-66-3, Gentamicin 1404-00-8, Mitomycin 1404-04-2, Neomycin 1404-90-6, Vancomycin 1405-87-4, Bacitracin 1405-97-6, Gramicidin 1406-11-7, Polymyxin 1406-16-2, Vitamin D 1406-18-4, Vitamin E 1407-73-4, Vitamin T 1538-09-6 1668-19-5, Doxepin 1695-77-8, Spectinomycin 1766-91-2, Penflutizide 1982-36-1, Homochlorcyclizine hydrochloride 1982-37-2, Methdilazine 2011-67-8, Nimetazepam 2013-58-3, Meclocycline 2020-25-9 2022-85-7, Flucytosine 2338-37-6, Levoproproxyphene 2398-96-1, Tolnaftate 2751-09-9, Troleandomycin 2751-68-0 3116-76-5, Dicloxacillin 3485-14-1 3562-84-3, Benzbromarone 3737-09-5, Disopyramide 3922-90-5, Oleandomycin 4205-90-7, Clonidine 4299-60-9, Sulfisoxazole diolamine 4342-03-4, DTIC 4502-14-1, Octopamine hydrochloride 4697-36-3, Carbenicillin 5536-17-4, Vidarabine 5588-33-0, Mesoridazine 6452-73-9, Oxprenolol hydrochloride 6493-05-6, Pentoxifylline 6834-98-6, Pentamycin 7195-27-9, Mefruside 7237-81-2, Hepronicate 7440-22-4D, Silver, salts 7440-45-1D, Cerium, salts 7440-66-6D, Zinc, salts 7487-94-7, Mercuric chloride, biological studies 7542-37-2
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(controlled-release transdermal pharmaceuticals contg. cryogels and)

IT 7722-64-7, Potassium permanganate 8017-57-0, Trisulfapyrimidine 8049-47-6, Pancreatin 9001-09-6, Chymopapain 9001-12-1, Collagenase 9001-73-4, Papain 9001-75-6, Pepsin 9001-90-5, Fibrinolysin

9001-98-3, Rennin 9002-01-1, Streptokinase 9002-07-7, Trypsin
9002-60-2, ACTH, biological studies 9002-64-6, Parathyrin 9002-71-5,
Thyrotropin 9002-72-6, Somatotropin 9003-98-9, Desoxyribonuclease
9004-07-3, Chymotrypsin 9004-10-8, Insulin, biological studies
9005-49-6, Heparin, biological studies 9007-12-9, Calcitonin
9015-68-3, Asparaginase 9039-53-6, Urokinase 10043-35-3, Boric acid,
biological studies 10118-90-8, Minocycline 10262-69-8, Maprotiline
10540-29-1, Tamoxifen 11000-17-2, Vasopressin 11011-73-7, Bramycin
11056-06-7, Bleomycin 11103-57-4, Vitamin A 11111-12-9, Cephalosporin
12001-76-2, Vitamin B 12001-79-5, Vitamin K 12211-28-8, Sutilains
12607-92-0, Aceglutamide aluminum 12629-01-5, Somatropin 13010-47-4,
CCNU 13171-25-0 13265-10-6, Methscopolamine 13292-46-1, Rifampin
13523-86-9, Pindolol 14838-15-4, Phenylpropanolamine 14929-11-4,
Simfibrate 15148-80-8, Bupranolol hydrochloride 15307-86-5, Diclofenac
15421-84-8, Trapidil 15663-27-1, cis-Platinum 15686-71-2, Cephalexin
15687-27-1, Ibuprofen 16051-77-7, Isosorbide-5-mononitrate 16110-51-3,
Cromolyn 17617-23-1, Flurazepam 17902-23-7, Tegafur 18323-44-9,
Clindamycin 18378-89-7, Plicamycin 18472-51-0, Chlorhexidine gluconate
19237-84-4, Prazosin hydrochloride 19504-77-9, Variotin 20153-98-4,
Dilazep dihydrochloride 20830-75-5, Digoxin 20830-81-3, Daunorubicin
21593-23-7, Cephapirin 21829-25-4 22071-15-4, Ketoprofen 22161-81-5,
S-Ketoprofen 22199-08-2, Silver sulfadiazine 22204-53-1 22494-42-4,
Diflunisal 22733-60-4, Siccanin 22916-47-8 23210-58-4, Ifenprodil
tartrate 23214-92-8, Doxorubicin 23593-75-1, **Clotrimazole**
25523-97-1, Dexchlorpheniramine 25655-41-8, Povidone iodine
25717-80-0, Molsidomine 25812-30-0, Gemfibrozil 25953-19-9, Cefazolin
25990-43-6, Mepenzolate 26328-04-1, Cinepazide maleate 26787-78-0,
Amoxicillin 27060-91-9, Flutazolam 27164-43-8 27321-61-5,
1,2,3-Propanetriolmononitrate 27724-96-5, Cetraxate hydrochloride
27959-26-8, Nicomol 28058-62-0 28088-64-4 28395-03-1 28657-80-9,
Cinoxacin 28911-01-5 29122-68-7, Atenolol 29868-97-1, Pirenzepine
hydrochloride 29975-16-4, Estazolam 30516-87-1, AZT 30685-43-9,
Metildigoxin 31879-05-7, Fenoprofen 32887-01-7, Amdinocillin
33069-62-4, Taxol 33286-22-5, Diltiazem hydrochloride 33419-42-0, VP16
33665-90-6 33671-46-4, Clotiazepam 34444-01-4, Cefamandole
34580-13-7, Ketotifen 34787-01-4 34915-68-9, Bunitrolol 35607-66-0,
Cefoxitin 37091-66-0, Azlocillin 37350-58-6, Metoprolol 37517-28-5,
Amikacin 38194-50-2, Sulindac 38821-53-3, Cephradine 50370-12-2,
Cefadroxil 50972-17-3, Bacampicillin 51481-61-9, Cimetidine
51481-65-3, Mezlocillin 51781-21-6, Carteolol hydrochloride
51940-44-4, Pipemidic acid 52663-81-7, Dobutamine hydrochloride
53608-75-6, Pancrelipase 53902-12-8, Tranilast 53994-73-3, Cefaclor
54527-84-3, Nicardipine hydrochloride 55268-75-2, Cefuroxime
55985-32-5, Nicardipine 56391-56-1, Netilmicin 56392-17-7, Metoprolol
tartrate 58001-44-8 59128-97-1, Haloxazolam 59277-89-3, Acyclovir
60925-61-3, Ceforanide 61270-58-4, Cefonicid 61422-45-5, Carmofur
61477-96-1, Piperacillin 62229-50-9, Epidermal growth factor
62683-29-8, CSF 62893-19-0, Cefoperazone 63527-52-6, Cefotaxime
64221-86-9, Imipenem 64952-97-2, Moxalactam 66676-88-8, Aclacinomycin
67763-96-6, IGF-1 68247-85-8, Peplomycin 68401-81-0, Ceftizoxime
70458-92-3 70458-96-7, Norfloxacin 72558-82-8, Ceftazidime
73384-59-5, Ceftriaxone 74011-58-8, Enoxacin 78186-34-2, Bisantrene
79217-60-0, Cyclosporin 79660-72-3, Fleroxacin 82009-34-5, Cilastatin
82030-87-3, Somatrem 82410-32-0, Gancyclovir 82419-36-1, Ofloxacin
82657-92-9, Pro-urokinase 83869-56-1, Colony-stimulating factor 2
84137-20-2, 1,2,3-Propanetriolnitrate 85721-33-1, Ciprofloxacin
98079-51-7, Lomefloxacin 100490-36-6 105636-15-5, Suprasec VM 25
118857-69-5D, alkyl derivs. 135968-09-1, RG-CSF 139639-23-9

150977-36-9, Bromelain
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(controlled-release transdermal pharmaceuticals contg. cryogels and)

L29 ANSWER 10 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB The role of various subfamilies of rat hepatic cytochrome P 450 in the oxidn. of theophylline was evaluated by comparing theophylline clearance in control rats and those pretreated with relatively selective inducers and inhibitors of the cytochromes P 450. Pretreatment with the CYP1A inducer, .beta.-naphthoflavone (BNF), increased theophylline clearance 4.5-fold ($p < 0.001$), and the CYP1A inhibitor, .alpha.-naphthoflavone, significantly attenuated the BNF effect. Pretreatment with phenobarbital, an inducer of CYP2B/C in rats, had a far more modest effect, increasing theophylline clearance only 1.6-fold ($p < 0.005$). The phenobarbital-mediated increase in theophylline clearance was attenuated by **orphenadrine**, a CYP2B/C inhibitor. The CYP2E inducer, isoniazid and the CYP2E inhibitor, diallyl sulfide were virtually without effect, as was the CYP4A inducer, clofibrate, and the CYP4A inhibitor, 10-undecynoic acid. Ajmaline, an inhibitor of CYP2D, was also without any effect on theophylline clearance. While the powerful CYP3A inducer **clotrimazole** did not increase theophylline clearance, toleandomycin, an inhibitor of CYP3A, did slow theophylline clearance by about 25% ($p < 0.002$). Together, these findings suggest that CYP1A is principally responsible for the overall oxidn. of theophylline in rats, and that CYP2B/C probably also mediates some theophylline oxidn. The involvement of CYP2D, CYP2E, CYP4A, and CYP3A is relatively trivial.

ACCESSION NUMBER: 1993:419901 CAPLUS
DOCUMENT NUMBER: 119:19901
TITLE: In vivo evidence that theophylline is metabolized principally by CYP1A in rats
AUTHOR(S): Bachmann, Kenneth; Sanyal, Gaurab; Potter, Jeffrey; Schiavone, Robert; Loch, Janette
CORPORATE SOURCE: Coll. Pharm., Univ. Toledo, Toledo, OH, 43606, USA
SOURCE: Pharmacology (**1993**), 47(1), 1-7
CODEN: PHMGBN; ISSN: 0031-7012
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Pharmacology (**1993**), 47(1), 1-7
CODEN: PHMGBN; ISSN: 0031-7012
AB The role of various subfamilies of rat hepatic cytochrome P 450 in the oxidn. of theophylline was evaluated by comparing theophylline clearance in control rats and those pretreated with relatively selective inducers and inhibitors of the cytochromes P 450. Pretreatment with the CYP1A inducer, .beta.-naphthoflavone (BNF), increased theophylline clearance 4.5-fold ($p < 0.001$), and the CYP1A inhibitor, .alpha.-naphthoflavone, significantly attenuated the BNF effect. Pretreatment with phenobarbital, an inducer of CYP2B/C in rats, had a far more modest effect, increasing theophylline clearance only 1.6-fold ($p < 0.005$). The phenobarbital-mediated increase in theophylline clearance was attenuated by **orphenadrine**, a CYP2B/C inhibitor. The CYP2E inducer, isoniazid and the CYP2E inhibitor, diallyl sulfide were virtually without effect, as was the CYP4A inducer, clofibrate, and the CYP4A inhibitor, 10-undecynoic acid. Ajmaline, an inhibitor of CYP2D, was also without any effect on theophylline clearance. While the powerful CYP3A inducer **clotrimazole** did not increase theophylline clearance, toleandomycin, an inhibitor of CYP3A, did slow theophylline clearance by about 25% ($p < 0.002$). Together, these findings suggest that CYP1A is principally responsible for the overall oxidn. of theophylline in rats,

and that CYP2B/C probably also mediates some theophylline oxidn. The involvement of CYP2D, CYP2E, CYP4A, and CYP3A is relatively trivial.

L29 ANSWER 11 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB The Ca2+-dependent K+ channel of human red cells was inhibited with high affinity by several imidazole antimycotics which are potent inhibitors of cytochrome P 450. IC50 values were (in .mu.M): **clotrimazole**, 0.05; tioconazole, 0.3; **miconazole**, 1.5; econazole, 1.8. Inhibition of the channel was also found with other drugs with known cytochrome P 450 inhibitory effect. However, no inhibition was obtained with carbon monoxide (CO). This suggests that, given the high selectivity of the above inhibitors for the heme moiety, a different but closely related to cytochrome P 450 kind of hemoprotein may be involved in the regulation of the red cell Ca2+-dependent K+ channel. **Clotrimazole** also inhibited two other charybdotoxin-sensitive Ca2+-dependent K+ channels, those of rat thymocytes (IC50 = 0.1-0.2 .mu.M) and of Ehrlich ascites tumor cells (IC50 = 0.5 .mu.M). Imidazole antimycotics inhibit also receptor-operated Ca2+ channels (M. Montero, et al., 1991). This suggests that both Ca2+ and Ca2+-dependent K+ channels might have a similar regulatory mechanism involving a cytochrome.

ACCESSION NUMBER: 1992:462387 CAPLUS
DOCUMENT NUMBER: 117:62387
TITLE: High affinity inhibition of calcium-dependent potassium channels by cytochrome P-450 inhibitors
AUTHOR(S): Alvarez, Javier; Montero, Mayte; Garcia-Sancho, Javier
CORPORATE SOURCE: Fac. Med., Univ. Valladolid, Valladolid, 47005, Spain
SOURCE: J. Biol. Chem. (**1992**), 267(17), 11789-93
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

SO J. Biol. Chem. (**1992**), 267(17), 11789-93
CODEN: JBCHA3; ISSN: 0021-9258

AB The Ca2+-dependent K+ channel of human red cells was inhibited with high affinity by several imidazole antimycotics which are potent inhibitors of cytochrome P 450. IC50 values were (in .mu.M): **clotrimazole**, 0.05; tioconazole, 0.3; **miconazole**, 1.5; econazole, 1.8. Inhibition of the channel was also found with other drugs with known cytochrome P 450 inhibitory effect. However, no inhibition was obtained with carbon monoxide (CO). This suggests that, given the high selectivity of the above inhibitors for the heme moiety, a different but closely related to cytochrome P 450 kind of hemoprotein may be involved in the regulation of the red cell Ca2+-dependent K+ channel. **Clotrimazole** also inhibited two other charybdotoxin-sensitive Ca2+-dependent K+ channels, those of rat thymocytes (IC50 = 0.1-0.2 .mu.M) and of Ehrlich ascites tumor cells (IC50 = 0.5 .mu.M). Imidazole antimycotics inhibit also receptor-operated Ca2+ channels (M. Montero, et al., 1991). This suggests that both Ca2+ and Ca2+-dependent K+ channels might have a similar regulatory mechanism involving a cytochrome.

IT 56-75-7, Chloramphenicol 58-73-1, Diphenhydramine 83-98-7, **Orphenadrine** 90-69-7, Lobeline 120-58-1, Isosafrole 519-23-3, Ellipticine 21829-25-4, Nifedipine 52468-60-7 66085-59-4, Nimodipine
RL: BIOL (Biological study)
(calcium-dependent calcium-dependent potassium channels of human in erythrocytes response to, cytochrome P 450 in relation to)

IT 22916-47-8, **Miconazole** 23593-75-1, **Clotrimazole** 27220-47-9, Econazole 65899-73-2, Tioconazole
RL: BIOL (Biological study)

(calcium-dependent potassium channel inhibition by, in human erythrocytes, cytochrome P 450 inhibition in relation to)

L29 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB Drugs in current clin. use were tested for anti-Leishmania activity using an in vitro infected macrophage assay. Out of almost 400 compds. tested, over 100 were active. The most active compds. showed ED50 values below 1 .mu.M. The active compds. should be tested in in vivo systems. They made lead to the development of new antileishmanials.

ACCESSION NUMBER: 1989:205119 CAPLUS
DOCUMENT NUMBER: 110:205119
TITLE: In vitro anti-leishmanial activity of compounds in current clinical use for unrelated diseases
AUTHOR(S): Neal, R. A.; Allen, S.
CORPORATE SOURCE: Dep. Med. Protozool., London Sch. Hyg. Trop. Med., St. Albans/Herts., UK
SOURCE: Drugs Exp. Clin. Res. (**1988**), 14(10), 621-8
CODEN: DECRDP; ISSN: 0378-6501
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Drugs Exp. Clin. Res. (**1988**), 14(10), 621-8
CODEN: DECRDP; ISSN: 0378-6501

IT 50-33-9, Phenylbutazone, biological studies 50-41-9, Clomiphene citrate 50-44-2 50-48-6, Amitriptyline 50-60-2, Phentolamine 50-65-7, Niclosamide 51-06-9, Procainamide 51-21-8, Fluorouracil 52-01-7, Spironolactone 52-24-4, Thiotepa 52-53-9, Verapamil 52-67-5, D-Penicillamine 52-86-8, Haloperidol 53-86-1, Indomethacin 54-31-9, Frusemide 54-32-0, Thymoxamine 54-36-4, Metyrapone 55-65-2, Guanethidine 55-73-2, Bethanidine 55-98-1 56-54-2, Quinidine 57-22-7, Vincristine 57-41-0, Phenytoin 57-66-9, Probenecid 57-96-5, Sulphinpyrazone 58-25-3, Chlordiazepoxide 58-32-2, Dipyridamole 58-39-9, Perphenazine 58-46-8, Tetrabenazine 58-54-8, Ethacrynic acid 58-55-9, biological studies 58-73-1 58-93-5, Hydrochlorothiazide 58-94-6, Chlorothiazide 59-05-2, Methotrexate 59-33-6, Mepyramine maleate 59-42-7, Phenylephrine 59-63-2, Isocarboxazide 59-66-5, Acetazolamide 59-92-7, Levodopa, biological studies 59-96-1, Phenoxybenzamine 60-80-0, Phenazone 60-87-7, Promethazine 61-56-3, Sulthiame 61-68-7, Mefenamic acid 61-75-6, Bretylium tosylate 64-77-7, Tolbutamide 65-29-2, Gallamine triethiodide 67-20-9, Nitrofurantoin 68-41-7, Cycloserine 68-88-2, Hydroxyzine 68-91-7 71-58-9 71-82-9, Levallorphan tartrate 72-69-5, Nortriptyline 72-80-0, Chlorquinaldol 73-48-3, Bendroflumethiazide 76-25-5, Triamcinolone acetonide 77-19-0, Dicyclomine 77-36-1, Chlorthalidone 77-37-2, Procyclidine 77-67-8, Ethosuximide 80-53-5, Terpin 80-77-3, Chlormezanone 81-81-2, Warfarin 82-92-8, Cyclizine 82-95-1, Buclizine 83-12-5, Phenindione 83-98-7, **Orphenadrine** 84-02-6, Prochlorperazine maleate 86-42-0, Amodiaquine 86-54-4, Hydralazine 90-82-4, Pseudoephedrine 91-33-8, Benzthiazide 92-12-6, Phenyltoloxamine 93-14-1, Guaiphenesin 93-30-1, Orthoxine 94-20-2, Chlorpropamide 94-78-0 97-77-8, Disulfiram 98-96-4, Pyrazinamide 110-85-0, Piperazine, biological studies 113-53-1, Dothiepin 113-59-7, Chlorprothixene 113-92-8, Chlorpheniramine maleate 114-07-8, Erythromycin 116-38-1, Edrophonium chloride 117-10-2, Danthron 118-42-3, Hydroxychloroquine 120-97-8 122-09-8, Phentermine 125-33-7, Primidone 125-64-4 125-71-3, Dextromethorphan 125-84-8, Aminoglutethimide 128-13-2, Ursodeoxycholic acid 129-03-3, Cyproheptadine 129-20-4, Oxyphenbutazone 132-17-2, Benztropine mesylate 132-20-7, Pheniramine maleate 135-07-9, Methyclothiazide

135-09-1, Hydroflumethiazide 144-11-6, Benzhexol 146-22-5, Nitrazepam 147-20-6, Diphenylpyraline 147-94-4, Cytarabine 148-79-8, Thiabendazole 148-82-3, Melphalan 154-21-2, Lincomycin 155-09-9, Tranylcypromine 155-97-5, Pyridostigmine 297-76-7, Ethynodiol diacetate 298-46-4, Carbamazepine 298-50-0, Propantheline 298-57-7, Cinnarizine 302-79-4, Tretinoin 305-03-3, Chlorambucil 309-29-5, Doxapram 322-35-0, Benserazide 339-44-6, Glymidine 346-18-9, Polythiazide 359-83-1, Pentazocine 361-37-5, Methysergide 364-62-5 364-98-7, Diazoxide 378-44-9 389-08-2, Nalidixic acid 390-28-3, Methoxamine 390-64-7, Prenylamine 395-28-8, Isoxsuprine 396-01-0 434-22-0, Nandrolone 437-38-7, Fentanyl 439-14-5, Diazepam 442-52-4, Clemizole 443-48-1 446-86-6 456-59-7, Cyclandelate 465-65-6, Naloxone 467-83-4, Dipipanone 469-62-5, Dextropropoxyphene 474-25-9, Chenodeoxycholic acid 479-18-5, Diprophylline 483-63-6, Crotamiton 486-12-4, Triprolidine 493-92-5, Prolintane 501-68-8, Beclamide 509-67-1, Pholcodine 512-15-2, Cyclopentolate 514-65-8, Biperiden 521-78-8, Trimipramine maleate 523-87-5, Dimenhydrinate 524-81-2 525-66-6 526-36-3, Xylometazoline 530-08-5, Isoetharine 532-03-6, Methocarbamol 533-45-9 548-73-2, Droperidol 555-30-6, Methyldopa 562-10-7 562-26-5, Phenoperidine 564-25-0, Doxycycline 569-59-5, Phenindamine 569-65-3, Meclozine 573-20-6, Acetomenaphthone 586-06-1, Orciprenaline 587-23-5, Methenamine mandelate 596-50-9, Poldine 596-51-0, Glycopyrrolate 604-75-1, Oxazepam 636-54-4, Clopamide 637-07-0, Clofibrate 638-23-3 642-72-8, Benzydamine 652-67-5, Isosorbide 671-16-9, Procarbazine 742-20-1, Cyclopenthiazide 751-94-0, Sodium fusidate 846-49-1, Lorazepam 846-50-4, Temazepam 848-75-9, Lormetazepam 865-21-4, Vinblastine 915-30-0, Diphenoxylate 968-81-0, Acetohexamide 980-71-2, Brompheniramine maleate 1066-17-7, Colistin 1082-57-1, Tramazoline 1131-64-2, Debrisoquine 1134-47-0, Baclofen 1143-38-0, Dithranol 1156-19-0, Tolazamide 1179-69-7, Thiethylperazine dimaleate 1197-18-8, Tranexamic acid 1404-88-2, Tyrothricin 1404-90-6, Vancomycin 1491-59-4, Oxymetazoline 1508-75-4, Tropicamide 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 1684-42-0, Acranil 1695-77-8, Spectinomycin 1812-30-2, Bromazepam 1951-25-3, Amiodarone 1954-28-5, Epodyl 2062-78-4, Pimozide 2062-84-2, Benperidol 2152-34-3, Pemoline 2169-75-7, Deptropine citrate 2347-80-0, Thioproperazine mesylate 2398-96-1, Tolnaftate 2609-46-3, Amiloride 2622-26-6, Pericyazine 2624-44-4, Ethamsylate 2809-21-4 2898-12-6, Medazepam 2955-38-6, Prazepam 3200-06-4, Naftidrofuryl oxalate 3416-26-0, Lidoflazine 3572-43-8, Bromhexine 3614-69-5, Dimethindene maleate 3625-06-7, Mebeverine 3688-62-8, Aminopromazine fumarate 3736-81-0, Diloxanide furoate 3737-09-5, Disopyramide 3778-73-2, Ifosfamide 3930-20-9, Sotalol 3978-86-7 4205-90-7, Clonidine 4330-99-8, Trimeprazine tartrate 4759-48-2, Isotretinoin 5003-48-5, Benorylate 5104-49-4 5118-30-9, Litracene 5534-09-8, Beclomethasone dipropionate 5536-17-4, Vidarabine 5560-59-8, Alverine citrate
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Leishmania donovani inhibition by)

IT 5638-76-6, Betahistine 6452-71-7, Oxprenolol 6493-05-6, Oxpentifylline 6506-37-2, Nimorazole 6556-11-2 6700-56-7, Ethoheptazine citrate 6740-88-1, Ketamine 7104-38-3, Methotrimeprazine maleate 7195-27-9, Mefruside 7261-97-4, Dantrolene 7492-32-2 7681-79-0, Etafedrine 7683-59-2, Isoprenaline 8067-24-1, Co-Dergocrine mesylate 9011-05-6, Polynoxylin 10040-45-6, Sodium picosulfate 10238-21-8, Glibenclamide 10262-69-8, Maprotiline 10418-03-8, Stanozolol 11056-06-7, Bleomycin 13115-40-7, Dimethothiazine mesylate 13392-18-2, Fenoterol 13473-38-6,

[redacted]

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=> s CYP2A6(p)(inhibit? or antagonist?) and (tobacco or smok? or
nicotine)(p)(addict? or withdrawal? or dependen? or behavio?)
           371 CYP2A6
       1488269 INHIBIT?
        181348 ANTAGONIST?
           160 CYP2A6(P)(INHIBIT? OR ANTAGONIST?)
         60442 TOBACCO
         49294 SMOK?
         23004 NICOTINE
          4904 ADDICT?
         28830 WITHDRAWAL?
       1367173 DEPENDEN?
        816048 BEHAVIO?
          9213 (TOBACCO OR SMOK? OR NICOTINE)(P)(ADDICT? OR WITHDRAWAL? OR
               DEPENDEN? OR BEHAVIO?)
L1            8 CYP2A6(P)(INHIBIT? OR ANTAGONIST?) AND (TOBACCO OR SMOK? OR
               NICOTINE)(P)(ADDICT? OR WITHDRAWAL? OR DEPENDEN? OR BEHAVIO?)

=> d l1 abs ibib kwic 1-8

L1   ANSWER 1 OF 8  CAPLUS  COPYRIGHT 2002 ACS
AB   Approx. 50% of the initiation of tobacco dependence is
     genetically influenced, whereas maintenance of dependent
     smoking behavior and amt. smoked have approx.
     70% genetic contribution (1-5). Detg. the variation in nicotine
     's inactivation is important because of nicotine's role in
     producing tobacco dependence and regulating
     smoking patterns (6-11). The genetically polymorphic
     CYP2A6 enzyme is responsible for the majority of the metabolic
     inactivation of nicotine to cotinine (12-14). Both in vitro and
     in vivo studies have demonstrated considerable interindividual variation
     in CYP2A6 activity (15-17). CYP2A6 is genetically
     polymorphic, individuals carrying inactive CYP2A6 alleles have
     decreased nicotine metab., are less likely to become
     smokers and if they do, they smoke fewer cigarettes per
     day (13, 18, 19). The decrease in smoking behavior
     was confirmed by measuring carbon monoxide (CO, a measure of smoke
     inhalation) levels, plasma and urine nicotine and cotinine
     levels, and cigarette counts (13, 18, 19). A duplication variant in the
     CYP2A6 gene locus has been identified which increases
     nicotine inactivation and increases smoking (19).
     CYP2A6 can also activate tobacco smoke
     procarcinogens (e.g. NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone);
     current studies are investigating the role of CYP2A6 in risk for
     lung cancer. Based on these epidemiol. data it was postulated that
     inhibition of CYP2A6 activity might be useful in a
     therapeutic context. Kinetic studies in humans indicated that selective
     CYP2A6 inhibitors decrease the metabolic removal of
     nicotine. It was also shown that inhibiting
     CYP2A6 in vivo (phenocopying, or mimicking the genetic defect) in
     smokers results in decreased smoking, making
     nicotine orally bioavailable, and the rerouting of procarcinogens
     to detoxifying pathways (20-22).
ACCESSION NUMBER:        2002:147172  CAPLUS
TITLE:                   Genetic variation in CYP2A6-mediated nicotine
                         metabolism alters smoking behavior
AUTHOR(S):               Tyndale, Rachel F.; Sellers, Edward M.
```

CORPORATE SOURCE: Center for Addictions and Mental Health, Toronto, ON, Can.
SOURCE: Therapeutic Drug Monitoring (2002), 24(1), 163-171
CODEN: TDMODV; ISSN: 0163-4356
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 141 THERE ARE 141 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Genetic variation in CYP2A6-mediated **nicotine** metabolism alters **smoking behavior**

AB Approx. 50% of the initiation of **tobacco dependence** is genetically influenced, whereas maintenance of **dependent smoking behavior** and amt. **smoked** have approx. 70% genetic contribution (1-5). Detg. the variation in **nicotine** 's inactivation is important because of **nicotine**'s role in producing **tobacco dependence** and regulating **smoking** patterns (6-11). The genetically polymorphic **CYP2A6** enzyme is responsible for the majority of the metabolic inactivation of **nicotine** to cotinine (12-14). Both in vitro and in vivo studies have demonstrated considerable interindividual variation in **CYP2A6** activity (15-17). **CYP2A6** is genetically polymorphic, individuals carrying inactive **CYP2A6** alleles have decreased **nicotine** metab., are less likely to become **smokers** and if they do, they **smoke** fewer cigarettes per day (13, 18, 19). The decrease in **smoking behavior** was confirmed by measuring carbon monoxide (CO, a measure of **smoke** inhalation) levels, plasma and urine **nicotine** and cotinine levels, and cigarette counts (13, 18, 19). A duplication variant in the **CYP2A6** gene locus has been identified which increases **nicotine** inactivation and increases **smoking** (19). **CYP2A6** can also activate **tobacco smoke** procarcinogens (e.g. NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone); current studies are investigating the role of **CYP2A6** in risk for lung cancer. Based on these epidemiol. data it was postulated that **inhibition** of **CYP2A6** activity might be useful in a therapeutic context. Kinetic studies in humans indicated that selective **CYP2A6 inhibitors** decrease the metabolic removal of **nicotine**. It was also shown that **inhibiting** **CYP2A6** in vivo (phenocopying, or mimicking the genetic defect) in **smokers** results in decreased **smoking**, making **nicotine** orally bioavailable, and the rerouting of procarcinogens to detoxifying pathways (20-22).

L1 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2002 ACS

AB **CYP2A6** is the principle enzyme metabolizing nicotine to its inactive metabolite cotinine. In this study, the selective probe reactions for each major cytochrome P 450 were used to evaluate the specificity and selectivity of the **CYP2A6 inhibitors** methoxsalen, tranylcypromine, and tryptamine in cDNA-expressing and human liver microsomes. Phenacetin O-deethylation (CYP1A2), coumarin 7-hydroxylation (**CYP2A6**), diclofenac 4'-hydroxylation (CYP2C9), omeprazole 5-hydroxylation (CYP2C19), dextromethorphan O-demethylation (CYP2D6), 7-ethoxy-4-trifluoromethylcoumarin deethylation (CYP2B6), p-nitrophenol hydroxylation (CYP2E1), and omeprazole sulfonation (CYP3A4) were used as index reactions. Apparent Ki values for **inhibition** of P450s' (1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4) activities showed

that tranylcypromine, methoxsalen, and tryptamine have high specificity and relative selectivity for **CYP2A6**. In cDNA-expressing microsomes, tranylcypromine **inhibited CYP2A6** (Ki = 0.08 .mu.M) with about 60- to 5000-fold greater potency relative to other P450s. Methoxsalen **inhibited CYP2A6** (Ki = 0.8 .mu.M) with about 3.5- 94-fold greater potency than other P450s, except for CYP1A2 (Ki = 0.2 .mu.M). Tryptamine **inhibited CYP2A6** (Ki = 1.7 .mu.M) with about 6.5- 213-fold greater potency relative to other P450s, except for CYP1A2 (Ki = 1.7 .mu.M). Similar results were also obtained with methoxsalen and tranylcypromine in human liver microsomes. R-(+)-Tranylcypromine, (.+-.)-tranylcypromine, and S-(-)-tranylcypromine competitively **inhibited CYP2A6** -mediated metab. of nicotine with apparent Ki values of 0.05, 0.08, and 2.0 .mu.M, resp. Tranylcypromine [particularly R-(+) isomer], tryptamine, and methoxsalen are specific and relatively selective for **CYP2A6** and may be useful in vivo to decrease smoking by **inhibiting** nicotine metab. with a low risk of metabolic drug interactions.

ACCESSION NUMBER: 2001:392449 CAPLUS
DOCUMENT NUMBER: 135:146768
TITLE: Evaluation of methoxsalen, tranylcypromine, and tryptamine as specific and selective **CYP2A6 inhibitors** in vitro
AUTHOR(S): Zhang, Wenjiang; Kilicarslan, Tansel; Tyndale, Rachel F.; Sellers, Edward M.
CORPORATE SOURCE: Department of Pharmacology, University of Toronto, Toronto, ON, Can.
SOURCE: Drug Metabolism and Disposition (2001), 29(6), 897-902 CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Evaluation of methoxsalen, tranylcypromine, and tryptamine as specific and selective **CYP2A6 inhibitors** in vitro

AB **CYP2A6** is the principle enzyme metabolizing nicotine to its inactive metabolite cotinine. In this study, the selective probe reactions for each major cytochrome P 450 were used to evaluate the specificity and selectivity of the **CYP2A6 inhibitors** methoxsalen, tranylcypromine, and tryptamine in cDNA-expressing and human liver microsomes. Phenacetin O-deethylation (CYP1A2), coumarin 7-hydroxylation (**CYP2A6**), diclofenac 4'-hydroxylation (CYP2C9), omeprazole 5-hydroxylation (CYP2C19), dextromethorphan O-demethylation (CYP2D6), 7-ethoxy-4-trifluoromethylcoumarin deethylation (CYP2B6), p-nitrophenol hydroxylation (CYP2E1), and omeprazole sulfonation (CYP3A4) were used as index reactions. Apparent Ki values for **inhibition** of P450s' (1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4) activities showed that tranylcypromine, methoxsalen, and tryptamine have high specificity and relative selectivity for **CYP2A6**. In cDNA-expressing microsomes, tranylcypromine **inhibited CYP2A6** (Ki = 0.08 .mu.M) with about 60- to 5000-fold greater potency relative to other P450s. Methoxsalen **inhibited CYP2A6** (Ki = 0.8 .mu.M) with about 3.5- 94-fold greater potency than other P450s, except for CYP1A2 (Ki = 0.2 .mu.M). Tryptamine **inhibited CYP2A6** (Ki = 1.7 .mu.M) with about 6.5- 213-fold greater potency relative to other P450s, except for CYP1A2 (Ki = 1.7 .mu.M). Similar results were also obtained with methoxsalen and tranylcypromine in human liver

microsomes. R-(+)-Tranylcypromine, (.+-.)-tranylcypromine, and S-(-)-tranylcypromine competitively **inhibited CYP2A6** -mediated metab. of nicotine with apparent Ki values of 0.05, 0.08, and 2.0 .mu.M, resp. Tranylcypromine [particularly R-(+) isomer], tryptamine, and methoxsalen are specific and relatively selective for **CYP2A6** and may be useful in vivo to decrease smoking by **inhibiting** nicotine metab. with a low risk of metabolic drug interactions.

ST cytochrome P4502A6 inhibitor methoxsalen tranylcypromine tryptamine **nicotine** metab; **smoking nicotine dependence** metab cytochrome P4502A6 tranylcypromine

IT Enzyme kinetics
(of **inhibition**; evaluation of methoxsalen, tranylcypromine, and tryptamine as specific and selective **CYP2A6 inhibitors** in vitro)

IT 61-54-1, Tryptamine 155-09-9, Tranylcypromine 298-81-7, Methoxsalen 3721-26-4, (-)-Tranylcypromine 3721-28-6, (+)-Tranylcypromine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(evaluation of methoxsalen, tranylcypromine, and tryptamine as specific and selective **CYP2A6 inhibitors** in vitro)

IT 54-11-5, Nicotine 329736-03-0, cytochrome P 450 3A4 329978-01-0, cytochrome P 450 2C9 330196-64-0, cytochrome P 450 1A2 330196-93-5, cytochrome P 450 2E1 330207-11-9, cytochrome P 450 2B6 330589-90-7, cytochrome P 450 2C19 330597-62-1, cytochrome P 450 2D6 331827-06-6, cytochrome P450 2A6
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(evaluation of methoxsalen, tranylcypromine, and tryptamine as specific and selective **CYP2A6 inhibitors** in vitro)

IT 486-56-6, Cotinine
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(evaluation of methoxsalen, tranylcypromine, and tryptamine as specific and selective **CYP2A6 inhibitors** in vitro)

L1 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2002 ACS

AB **Nicotine** is the psychoactive substance responsible for **tobacco dependence**; **smokers** adjust their cigarette consumption to maintain brain **nicotine** levels. In humans, 70 to 80% of **nicotine** is metabolized to the inactive metabolite cotinine by the enzyme **CYP2A6**. **CYP2A6** can also activate **tobacco smoke** procarcinogens [e.g., NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone]. In initial studies we found that there was an under-representation of individuals carrying defective **CYP2A6** alleles in a **tobacco-dependent** population, and that among **smokers**, those with deficient **nicotine** metab. **smoked** fewer cigarettes. We have since reproduced this data in a prospective **smoking** study (400 male and female, heavy and light **smokers**) examg. the role of the **CYP2A6** genotype on carbon monoxide levels, plasma and urine **nicotine** and cotinine levels, and cigarette counts. We have also recently identified deletion and duplication variants in the **CYP2A6** gene locus and have examd. their impact on **smoking**. These data provide the impetus to examine how **inhibition** of **CYP2A6** activity might be useful in a therapeutic context. Both kinetic and **behavioral** expts. in human **smokers** demonstrated that **inhibiting CYP2A6** in vivo decreased **nicotine** metab. and **smoking behavior**. This

article summarizes the preliminary results from our studies.

ACCESSION NUMBER: 2001:266517 CAPLUS
DOCUMENT NUMBER: 134:337081
TITLE: Variable CYP2A6-mediated **nicotine** metabolism alters **smoking behavior** and risk
AUTHOR(S): Tyndale, Rachel F.; Sellers, Edward M.
CORPORATE SOURCE: Centre for Addictions and Mental Health, Toronto, ON, Can.
SOURCE: Drug Metabolism and Disposition (2001), 29(4, Pt. 2), 548-552
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Variable CYP2A6-mediated **nicotine** metabolism alters **smoking behavior** and risk

AB **Nicotine** is the psychoactive substance responsible for **tobacco dependence**; **smokers** adjust their cigarette consumption to maintain brain **nicotine** levels. In humans, 70 to 80% of **nicotine** is metabolized to the inactive metabolite cotinine by the enzyme **CYP2A6**. **CYP2A6** can also activate **tobacco smoke** procarcinogens [e.g., NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone]. In initial studies we found that there was an under-representation of individuals carrying defective **CYP2A6** alleles in a **tobacco-dependent** population, and that among **smokers**, those with deficient **nicotine** metab. **smoked** fewer cigarettes. We have since reproduced this data in a prospective **smoking** study (400 male and female, heavy and light **smokers**) examg. the role of the **CYP2A6** genotype on carbon monoxide levels, plasma and urine **nicotine** and cotinine levels, and cigarette counts. We have also recently identified deletion and duplication variants in the **CYP2A6** gene locus and have examd. their impact on **smoking**. These data provide the impetus to examine how **inhibition** of **CYP2A6** activity might be useful in a therapeutic context. Both kinetic and **behavioral** expts. in human **smokers** demonstrated that **inhibiting CYP2A6** in vivo decreased **nicotine** metab. and **smoking behavior**. This article summarizes the preliminary results from our studies.

ST CYP2A6 **nicotine** metab **smoking behavior** review

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CYP2A6; variable CYP2A6-mediated **nicotine** metab. alters **smoking behavior** and risk)

IT **Tobacco** products
(cigarettes, no. **smoked**; variable CYP2A6-mediated **nicotine** metab. alters **smoking behavior** and risk)

IT **Behavior**
(**smoking**; variable CYP2A6-mediated **nicotine** metab. alters **smoking behavior** and risk)

IT Genotypes
Tobacco smoke

[redacted]

Urine
(variable CYP2A6-mediated **nicotine** metab. alters **smoking behavior** and risk)

IT 331827-06-6, Cytochrome p 450 2A6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(variable CYP2A6-mediated **nicotine** metab. alters **smoking behavior** and risk)

IT 54-11-5, **Nicotine**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(variable CYP2A6-mediated **nicotine** metab. alters **smoking behavior** and risk)

IT 486-56-6, Cotinine
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(variable CYP2A6-mediated **nicotine** metab. alters **smoking behavior** and risk)

IT 630-08-0, Carbon monoxide, biological studies
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(variable CYP2A6-mediated **nicotine** metab. alters **smoking behavior** and risk)

L1 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2002 ACS

AB **Nicotine** establishes and maintains **tobacco dependence**. Individuals with genetically deficient **CYP2A6 nicotine** metab. are at lower risk to become **smokers** and, if **dependent**, will **smoke** fewer cigarettes. Hepatic **CYP2A6** accounts for **nicotine**'s low systemic bioavailability, precluding oral **nicotine** replacement to treat **dependence**. We sought to det. whether **CYP2A6 inhibition** via oral methoxsalen decreases **nicotine** clearance, increases **nicotine** bioavailability, and decreases **smoking**. Two within-subject designs in healthy **tobacco-dependent** volunteers were conducted: a single-blind kinetic study (n = 17) of methoxsalen 30, 10, or 3.5 mg or placebo given with **nicotine** 4 mg orally to abstinent **smokers**; and a double-blind randomized crossover study (n = 11) of methoxsalen 30 mg or placebo crossed with **nicotine** 4 mg given orally or placebo before 60 min' abstinence and 90 min' free **smoking**. Placebo plus **nicotine** 4 mg orally increased the mean 3-h plasma **nicotine** level by 4 ng/mL over residual baseline **nicotine** level, whereas methoxsalen 10 or 30 mg plus **nicotine** increased it by 9 ng/mL ($P < .01$), demonstrating in vivo **inhibition** of **CYP2A6 nicotine** metab. Methoxsalen 30 mg plus **nicotine** 4 mg given orally decreased breath carbon monoxide concn. at the end of free **smoking** by 47% (4.6 vs. 8.7 ppm; $P < .01$) and cigarettes **smoked** by 24% (3.1 vs. 4.1, $P < .01$) compared with placebo plus placebo. Methoxsalen **inhibits nicotine** first-pass metab. of orally administered **nicotine**, and the combination directly reduces **smoking** in a lab. setting. **CYP2A6 inhibitors** may have an important role in **smoking** cessation and **tobacco** exposure redn.

ACCESSION NUMBER: 2000:587818 CAPLUS
DOCUMENT NUMBER: 134:36914
TITLE: Inhibition of cytochrome P450 2A6 increases nicotine's

oral bioavailability and decreases smoking

AUTHOR(S): Sellers, Edward M.; Kaplan, Howard L.; Tyndale, Rachel F.
CORPORATE SOURCE: Departments of Pharmacology, Medicine, University of Toronto, Toronto, ON, Can.
SOURCE: Clinical Pharmacology & Therapeutics (St. Louis) (2000), 68(1), 35-43
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB **Nicotine** establishes and maintains **tobacco dependence**. Individuals with genetically deficient **CYP2A6** **nicotine** metab. are at lower risk to become **smokers** and, if **dependent**, will **smoke** fewer cigarettes. Hepatic **CYP2A6** accounts for **nicotine**'s low systemic bioavailability, precluding oral **nicotine** replacement to treat **dependence**. We sought to det. whether **CYP2A6** **inhibition** via oral methoxsalen decreases **nicotine** clearance, increases **nicotine** bioavailability, and decreases **smoking**. Two within-subject designs in healthy **tobacco-dependent** volunteers were conducted: a single-blind kinetic study (n = 17) of methoxsalen 30, 10, or 3.5 mg or placebo given with **nicotine** 4 mg orally to abstinent **smokers**; and a double-blind randomized crossover study (n = 11) of methoxsalen 30 mg or placebo crossed with **nicotine** 4 mg given orally or placebo before 60 min' abstinence and 90 min' free **smoking**. Placebo plus **nicotine** 4 mg orally increased the mean 3-h plasma **nicotine** level by 4 ng/mL over residual baseline **nicotine** level, whereas methoxsalen 10 or 30 mg plus **nicotine** increased it by 9 ng/mL ($P < .01$), demonstrating in vivo **inhibition** of **CYP2A6** **nicotine** metab. Methoxsalen 30 mg plus **nicotine** 4 mg given orally decreased breath carbon monoxide concn. at the end of free **smoking** by 47% (4.6 vs. 8.7 ppm; $P < .01$) and cigarettes **smoked** by 24% (3.1 vs. 4.1, $P < .01$) compared with placebo plus placebo. Methoxsalen **inhibits** **nicotine** first-pass metab. of orally administered **nicotine**, and the combination directly reduces **smoking** in a lab. setting. **CYP2A6** **inhibitors** may have an important role in **smoking** cessation and **tobacco** exposure redn.

ST methoxsalen **nicotine** oral bioavailability CYP4502A6 **tobacco dependence**; **smoking** cessation methoxsalen **nicotine** interaction CYP2A6

IT Tobacco smoke
(cessation of; role of **CYP2A6** **inhibitors** in smoking cessation)

IT Drug bioavailability
(oral; role of **CYP2A6** **inhibitors** in smoking cessation)

IT Blood plasma
Drug **dependence**
Drug interactions
Drug metabolism
(role of **CYP2A6** **inhibitors** in **smoking** cessation)

IT Drug **withdrawal**

(**tobacco**; role of **CYP2A6 inhibitors** in **smoking** cessation)

IT 9035-51-2, Cytochrome P450, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(2A6; role of **CYP2A6 inhibitors** in smoking cessation)

IT 54-11-5, Nicotine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(role of **CYP2A6 inhibitors** in smoking cessation)

IT 298-81-7, Methoxsalen
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(role of **CYP2A6 inhibitors** in smoking cessation)

IT 630-08-0, Carbon monoxide, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(role of **CYP2A6 inhibitors** in smoking cessation)

L1 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2002 ACS

AB A review with 60 refs. including the authors own work is given. The genetic basis for drug **dependence** has focused on genes that encode receptors involved in the reinforcing properties of drugs of abuse or that det. drug-taking **behavior** (e.g. impulsivity, etc.). Pharmacogenetic variations in the patterns of metab. among individuals can also importantly modulate the risk of drug **dependence**. Cytochrome P 450 drug metabolizing enzymes (CYPs), can activate (e.g. codeine to morphine) or deactivate (e.g. **nicotine** to cotinine) drugs of abuse. Some CYPs are polymorphic, i.e., there are gene mutations which result in individuals with no (null mutations) or decreased enzyme activity (e.g. CYP2D6*10). Individuals with 2 null mutations appear in the population as phenotypic poor metabolizers. Using in vitro studies, the authors have identified drugs of abuse that are substrates of the polymorphic enzymes CYP2D6 (codeine, amphetamines, dextromethorphan), **CYP2A6** (**nicotine**), and CYP2C19 (flunitrazepam). In human exptl. studies, the authors have shown that CYP phenotype and genotype affect abuse liability of CYP2D6 metabolized drugs of abuse. In addn., the authors **inhibited** CYP2D6 and decreased individuals' risk of **dependence** exptl. (codeine, dextromethorphan) and treated codeine **dependence**. In epidemiol. studies CYP2D6 and **CYP2A6** null mutations protect individuals from becoming codeine and **tobacco dependent**, resp. With respect to **CYP2A6**, individuals with mutations, **smoke** fewer cigarettes and can quit more easily. **Inhibiting CYP2A6** (e.g. tranylcypromine, methoxsalen) decreases **smoking** and the activation of procarcinogens. By mimicking these gene defects the risk of **dependence** can be decreased in individuals and new treatments developed.

ACCESSION NUMBER: 2000:547073 CAPLUS
DOCUMENT NUMBER: 134:42
TITLE: Mimicking gene defects to treat drug dependence
AUTHOR(S): Sellers, Edward M.; Tyndale, Rachel F.
CORPORATE SOURCE: Department of Pharmacology, University of Toronto, Toronto, ON, M5S 1B2, Can.

SOURCE: Annals of the New York Academy of Sciences (2000), 909(New Medications for Drug Abuse), 233-246
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review with 60 refs. including the authors own work is given. The genetic basis for drug **dependence** has focused on genes that encode receptors involved in the reinforcing properties of drugs of abuse or that det. drug-taking **behavior** (e.g. impulsivity, etc.). Pharmacogenetic variations in the patterns of metab. among individuals can also importantly modulate the risk of drug **dependence**. Cytochrome P 450 drug metabolizing enzymes (CYPs), can activate (e.g. codeine to morphine) or deactivate (e.g. **nicotine** to cotinine) drugs of abuse. Some CYPs are polymorphic, i.e., there are gene mutations which result in individuals with no (null mutations) or decreased enzyme activity (e.g. CYP2D6*10). Individuals with 2 null mutations appear in the population as phenotypic poor metabolizers. Using in vitro studies, the authors have identified drugs of abuse that are substrates of the polymorphic enzymes CYP2D6 (codeine, amphetamines, dextromethorphan), **CYP2A6** (**nicotine**), and CYP2C19 (flunitrazepam). In human exptl. studies, the authors have shown that CYP phenotype and genotype affect abuse liability of CYP2D6 metabolized drugs of abuse. In addn., the authors **inhibited** CYP2D6 and decreased individuals' risk of **dependence** exptl. (codeine, dextromethorphan) and treated codeine **dependence**. In epidemiol. studies CYP2D6 and **CYP2A6** null mutations protect individuals from becoming codeine and **tobacco dependent**, resp. With respect to **CYP2A6**, individuals with mutations, **smoke** fewer cigarettes and can quit more easily. **Inhibiting CYP2A6** (e.g. tranylcypromine, methoxsalen) decreases **smoking** and the activation of procarcinogens. By mimicking these gene defects the risk of **dependence** can be decreased in individuals and new treatments developed.

L1 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2002 ACS

AB A review and discussion with 36 refs. Pharmacogenetic variations in the patterns of metab. among individuals can importantly modulate the risk of drug **dependence**. Cytochrome P 450 drug metabolizing enzymes (CYPs), can activate drugs of abuse (e.g., codeine to morphine) or deactivate drugs (e.g., **nicotine** to cotinine). Some CYPs are polymorphic, i.e., there are gene mutations which result in no active enzyme (null mutations). Individuals with two null mutations appear in the population as phenotypic poor metabolizers. Using in vitro studies, we have identified drugs of abuse that are substrates of the polymorphic enzymes CYP2D6, **CYP2A6** and CYP2C19. In human exptl. studies, we have shown that CYP phenotype and genotype affect abuse liability for CYP2D6 metabolized drugs of abuse. In addn., we **inhibited** CYP2D6 and decreased individuals' risk of **dependence** exptl. and in treating codeine **dependence**. In epidemiol. studies CYP2D6 and **CYP2A6** null mutations protect individuals from becoming codeine and **tobacco dependent**, resp. With respect to **CYP2A6**, heterozygote individuals, if they become **smokers**, **smoke** about 25% fewer cigarettes because of their slower **nicotine** metab. Since normally occurring mutations in CYP alleles decrease the risk of **dependence**, pharmacol. modification of CYP

activity has the potential to prevent and treat drug **dependence**.

ACCESSION NUMBER: 1999:637970 CAPLUS
DOCUMENT NUMBER: 132:131586
TITLE: Pharmacogenetic basis of variation in drug dependence
AUTHOR(S): Sellers, Edward M.; Romach, Myroslava K.; Tyndale, Rachel F.
CORPORATE SOURCE: Departments of Pharmacology, Medicine and Psychiatry, University of Toronto, Toronto, ON, M5S 1A8, Can.
SOURCE: International Congress Series (1999), 1178(Variability in Human Drug Response), 219-229
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review and discussion with 36 refs. Pharmacogenetic variations in the patterns of metab. among individuals can importantly modulate the risk of drug **dependence**. Cytochrome P 450 drug metabolizing enzymes (CYPs), can activate drugs of abuse (e.g., codeine to morphine) or deactivate drugs (e.g., **nicotine** to cotinine). Some CYPs are polymorphic, i.e., there are gene mutations which result in no active enzyme (null mutations). Individuals with two null mutations appear in the population as phenotypic poor metabolizers. Using in vitro studies, we have identified drugs of abuse that are substrates of the polymorphic enzymes CYP2D6, **CYP2A6** and CYP2C19. In human exptl. studies, we have shown that CYP phenotype and genotype affect abuse liability for CYP2D6 metabolized drugs of abuse. In addn., we **inhibited** CYP2D6 and decreased individuals' risk of **dependence** exptl. and in treating codeine **dependence**. In epidemiol. studies CYP2D6 and **CYP2A6** null mutations protect individuals from becoming codeine and **tobacco dependent**, resp. With respect to **CYP2A6**, heterozygote individuals, if they become **smokers**, **smoke** about 25% fewer cigarettes because of their slower **nicotine** metab. Since normally occurring mutations in CYP alleles decrease the risk of **dependence**, pharmacol. modification of CYP activity has the potential to prevent and treat drug **dependence**.

L1 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2002 ACS

AB A method of regulating the activity of human cytochrome P 450 isoenzyme **CYP2A6** to control **nicotine** metab. or decrease the prodn. of carcinogens from procarcinogens, such as those present in **tobacco smoke**, in an individual by selectively **inhibiting CYP2A6**. Various prophylactic (i.e., prevention and treatment) compns. and methods are also described, including an improved oral **nicotine** compn. and method comprising the use of **nicotine** together with an **inhibitor** of the **CYP2A6** enzyme. Furthermore, it has been discovered that the presence in an individual of a mutant allele of human cytochrome P 450 enzyme **CYP2A6** (referred to throughout this specification as "**CYP2A6**" for brevity) is predictive of an individual who: (i) has a decreased risk of becoming a **smoker**, (ii) will **smoke** less if he/she becomes **dependent**, and/or (iii) may be at relatively lower risk for cancer due to both decreased **smoke** exposure and decreased **CYP2A6**-mediated activation of **tobacco smoke** and other procarcinogenic substrates. This invention provides diagnostic methods for predicting **tobacco dependence** risk and risk for cancers related to **CYP2A6**

substrates in an individual by analyzing for the presence of a mutant genotype for human cytochrome P 450 enzyme **CYP2A6** in an individual, ranging from gene duplication (multiple copies of **CYP2A6**) to single or even no copies due to null alleles or gene deletion.

ACCESSION NUMBER: 1999:372066 CAPLUS
DOCUMENT NUMBER: 131:15139
TITLE: Therapeutic and diagnostic methods dependent on CYP2A enzymes
INVENTOR(S): Sellers, Edward M.; Tyndale, Rachel F.
PATENT ASSIGNEE(S): Nicogen Inc., Can.
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9927919	A2	19990610	WO 1998-CA1093	19981201
WO 9927919	A3	19990812		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
WO 9803171	A2	19980129	WO 1997-CA506	19970717
WO 9803171	A3	19980226		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2312851	AA	19990610	CA 1998-2312851	19981201
AU 9913286	A1	19990616	AU 1999-13286	19981201
EP 1033979	A2	20000913	EP 1998-956735	19981201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 9815128	A	20001010	BR 1998-15128	19981201
JP 2001524516	T2	20011204	JP 2000-522905	19981201

PRIORITY APPLN. INFO.:		
WO 1997-CA506	A2	19970717
US 1997-67020P	P	19971201
US 1997-67021P	P	19971201
US 1998-84847P	P	19980508
US 1998-107392P	P	19981106
US 1996-21940P	P	19960717
WO 1998-CA1093	W	19981201

AB A method of regulating the activity of human cytochrome P 450 isoenzyme **CYP2A6** to control **nicotine** metab. or decrease the prodn. of carcinogens from procarcinogens, such as those present in **tobacco smoke**, in an individual by selectively

inhibiting CYP2A6. Various prophylactic (i.e., prevention and treatment) compns. and methods are also described, including an improved oral **nicotine** compn. and method comprising the use of **nicotine** together with an **inhibitor** of the **CYP2A6** enzyme. Furthermore, it has been discovered that the presence in an individual of a mutant allele of human cytochrome P 450 enzyme **CYP2A6** (referred to throughout this specification as "**CYP2A6**" for brevity) is predictive of an individual who: (i) has a decreased risk of becoming a **smoker**, (ii) will **smoke** less if he/she becomes **dependent**, and/or (iii) may be at relatively lower risk for cancer due to both decreased **smoke** exposure and decreased **CYP2A6**-mediated activation of **tobacco smoke** and other procarcinogenic substrates. This invention provides diagnostic methods for predicting **tobacco dependence** risk and risk for cancers related to **CYP2A6** substrates in an individual by analyzing for the presence of a mutant genotype for human cytochrome P 450 enzyme **CYP2A6** in an individual, ranging from gene duplication (multiple copies of **CYP2A6**) to single or even no copies due to null alleles or gene deletion.

L1 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2002 ACS

AB Comparison of 7-hydroxylation of coumarin, a **CYP2A6** substrate, in human and African green and cynomolgus monkey liver microsomes was made by an HPLC assay with UV detection. In human liver microsomes, the Km and Vmax values for the metabolic conversion were 2.1 .mu.M and 0.79 nmol/mg/min, resp. While African green monkey showed Km and Vmax values of 2.7 .mu.M and 0.52 nmol/mg/min, which were similar to human, higher Km and Vmax values were found in cynomolgus monkey. Coumarin 7-hydroxylation in human and African green monkey was selectively **inhibited** by methoxsalen and pilocarpine (**CYP2A6 inhibitors**) but not by other **inhibitors**, i.e. .alpha.-naphthoflavone (CYP1A1), orphenadrine (CYP2B6), sulfaphenazole (CYP2C9), quinidine (CYP2D6), and ketoconazole (CYP3A4). Immunoinhibition results supported **CYP2A6** involvement in human and its homolog in monkey in coumarin 7-hydroxylation, as only anti-**CYP2A6**, but not CYP2B1, CYP2C13, CYP2D6, CYP2E1, or CYP3A antibodies, **inhibited** this conversion. African green monkey was similar to human in catalytic activity of coumarin 7-hydroxylation and response to **CYP2A6 inhibitors** or antibody **inhibition**. However, the monkey **CYP2A6** is not identical to the human in that Ki values were different, and differences were obsd. with some **CYP2A6 inhibitors**, such as **nicotine** and methoxsalen, suggesting that, under some circumstances, studies of **nicotine** kinetics and drug taking **behavior** in monkey may not be comparable to human.

ACCESSION NUMBER: 1998:150136 CAPLUS
DOCUMENT NUMBER: 128:164257
TITLE: Comparison of CYP2A6 catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes
AUTHOR(S): Li, Yan; Li, Ning Yuan; Sellers, Edward M.
CORPORATE SOURCE: Dep. Pharmacology, Medicine, Psychiatry, Univ. Toronto, Toronto, ON, M5S 1A8, Can.
SOURCE: European Journal of Drug Metabolism and Pharmacokinetics (1997), 22(4), 295-304
CODEN: EJDPD2; ISSN: 0378-7966
PUBLISHER: Medecine et Hygiene
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Comparison of 7-hydroxylation of coumarin, a **CYP2A6** substrate, in human and African green and cynomolgus monkey liver microsomes was made by an HPLC assay with UV detection. In human liver microsomes, the Km and Vmax values for the metabolic conversion were 2.1 .mu.M and 0.79 nmol/mg/min, resp. While African green monkey showed Km and Vmax values of 2.7 .mu.M and 0.52 nmol/mg/min, which were similar to human, higher Km and Vmax values were found in cynomolgus monkey. Coumarin 7-hydroxylation in human and African green monkey was selectively **inhibited** by methoxsalen and pilocarpine (**CYP2A6 inhibitors**) but not by other **inhibitors**, i.e. .alpha.-naphthoflavone (CYP1A1), orphenadrine (CYP2B6), sulfaphenazole (CYP2C9), quinidine (CYP2D6), and ketoconazole (CYP3A4). Immunoinhibition results supported **CYP2A6** involvement in human and its homolog in monkey in coumarin 7-hydroxylation, as only anti-**CYP2A6**, but not CYP2B1, CYP2C13, CYP2D6, CYP2E1, or CYP3A antibodies, **inhibited** this conversion. African green monkey was similar to human in catalytic activity of coumarin 7-hydroxylation and response to **CYP2A6** **inhibitors** or antibody **inhibition**. However, the monkey **CYP2A6** is not identical to the human in that Ki values were different, and differences were obsd. with some **CYP2A6** **inhibitors**, such as **nicotine** and methoxsalen, suggesting that, under some circumstances, studies of **nicotine** kinetics and drug taking **behavior** in monkey may not be comparable to human.

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(monoclonal; selective **inhibition** of coumarin 7-hydroxylation by **CYP2A6** monoclonal antibody)

=>

Pipenzolate 13523-86-9, Pindolol 13539-59-8, Azapropazone 13647-35-3, Trilostane 13669-70-0, Nefopam 14007-64-8, Butethamate 14293-44-8, Xipamide 14611-51-9, Selegiline 14759-06-9, Sulforidazine 14838-15-4, Phenylpropanolamine 14976-57-9 15301-93-6, Tofenacin 15307-86-5, Diclofenac 15351-13-0, Nicofuranose 15574-96-6, Pizotifen 15599-39-0, Noxytiolin 15663-27-1, Cisplatin 15676-16-1, Sulpiride 15687-27-1, Ibuprofen 15826-37-6, Sodium cromoglycate 17560-51-9, Metolazone 17617-23-1, Flurazepam 18378-89-7, Mithramycin 18559-94-9, Salbutamol 18833-13-1 19216-56-9, Prazosin 19387-91-8, Tinidazole 19388-87-5 19794-93-5, Trazodone 21829-25-4, Nifedipine 22071-15-4, Ketoprofen 22204-24-6, Pyrantel pamoate 22204-53-1, Naproxen 22232-54-8, Carbimazole 22232-71-9, Mazindol 22254-24-6, Ipratropium bromide 22316-47-8, Clobazam 23031-25-6, Terbutaline 23047-25-8, Lofepramine 23214-92-8 23288-49-5, Probucol 23593-75-1, **Clotrimazole** 23887-31-2, Clorazepate 24219-97-4, Mianserin 25953-19-9, Cefazolin 25990-43-6, Mepenzolate 26171-23-3, Tolmetin 26652-09-5, Ritodrine 26844-12-2, Indoramin 26921-17-5, Timolol maleate 26944-48-9, Glibornuride 28395-03-1, Bumetanide 28657-80-9, Cinoxacin 28797-61-7, Pirenzepine 28911-01-5, Triazolam 28981-97-7, Alprazolam 29094-61-9, Glipizide 29122-68-7, Atenolol 29216-28-2, Mequitazine 31431-39-7, Mebendazole 31828-71-4, Mexiletine 31879-05-7, Fenoprofen 32795-47-4, Nomifensine hydrogen maleate 32887-01-7, Mecillinam 32953-89-2, Rimiterol 32986-56-4, Tobramycin 33005-95-7, Tiaprofenic acid 33402-03-8 33419-42-0, Etoposide 34368-04-2, Dobutamine 34444-01-4, Cefamandole 34580-14-8, Ketotifen hydrogen fumarate 35607-66-0, Cefoxitin 35941-65-2, Butriptyline 36322-90-4, Piroxicam 36330-85-5, Fenbufen 36894-69-6, Labetalol 37270-89-6, Calcium heparin 37517-30-9, Acebutolol 38194-50-2, Sulindac 38304-91-5, Minoxidil 38363-40-5, Penbutolol 38677-81-5, Pirbuterol 38821-53-3, Cephradine 40034-42-2, Acrosoxacin 40828-46-4, Suprofen 41708-72-9, Tocainide 41859-67-0, Bezafibrate 42200-33-9, Nadolol 46817-91-8, Viloxazine 50370-12-2, Cefadroxil 50679-08-8, Terfenadine 51022-71-0, Nabilone 51481-65-3, Mezlocillin 52485-79-7, Buprenorphine 53179-11-6, Loperamide 53772-82-0, cis-Flupenthixol 53772-83-1, Zuclopenthixol 53772-84-2 53772-85-3, trans-Flupenthixol 53994-73-3 54143-56-5, Flecainide acetate 54340-58-8, Meptazinol 54350-48-0, Etretinate 54965-24-1, Tamoxifen citrate 55837-27-9, Piretanide 56391-56-1, Netilmicin 56392-17-7, Metoprolol tartrate 57526-81-5, Prenalterol 57808-66-9, Domperidone 59277-89-3, Acyclovir 59467-70-8, Midazolam 59865-13-3, Cyclosporin A 60607-34-3, Oxatomide 61197-73-7, Loprazolam 62571-86-2, Captopril 62587-73-9, Cefsulodin 63527-52-6, Cefotaxime 64228-81-5, Atracurium besylate 64952-97-2, Moxalactam 66357-35-5 68401-81-0, Ceftizoxime 68844-77-9, Astemizole 70052-12-9 71195-58-9, Alfentanil
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Leishmania donovani inhibition by)

L29 ANSWER 13 OF 24 CAPLUS COPYRIGHT 2002 ACS
AB The principal components (PC) anal. of standardized Rf values in 4 eluent systems [ethyl acetate-methanol-30% ammonia (85:10:15), cyclohexane-toluene-diethylamine (65:25:10), Et acetate-chloroform (50:50), and acetone with the plate dipped in KOH soln.] and of gas chromatog. retention indexes in SE 30 for 277 compds. provided a 2-PC model that explains 82% of the total variance. The scores plot allowed identification of unknowns or restriction of the range of inquiry to very few candidates. Comparison of these candidates with those selected from another PC model derived from thin-layer chromatog. data only allowed

identification of the drug in all the examd. cases.

ACCESSION NUMBER: 1987:526383 CAPLUS
DOCUMENT NUMBER: 107:126383
TITLE: Qualitative organic analysis. Part 2. Identification of drugs by principal components analysis of standardized TLC data in four eluent systems and of retention indexes on SE 30
AUTHOR(S): Musumarra, Giuseppe; Scarlata, Giuseppe; Romano, Guido; Cappello, Giuseppe; Clementi, Sergio; Giulietti, Gianfranco
CORPORATE SOURCE: Dip. Sci. Chim., Univ. Catania, Catania, 95125, Italy
SOURCE: J. Anal. Toxicol. (**1987**), 11(4), 154-63
CODEN: JATOD3; ISSN: 0146-4760
DOCUMENT TYPE: Journal
LANGUAGE: English
SO J. Anal. Toxicol. (**1987**), 11(4), 154-63
CODEN: JATOD3; ISSN: 0146-4760
IT 50-36-2, Cocaine 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-52-2, Thioridazine 50-53-3, Chlorpromazine, biological studies 50-58-8, Phendimetrazine bitartrate 51-34-3, Scopolamine 51-55-8, Atropine, biological studies 51-68-3, Meclofenoxate 52-53-9, Verapamil 52-86-8, Haloperidol 54-05-7, Chloroquine 54-11-5, Nicotine 54-32-0, Moxisylyte 54-85-3 56-54-2, Quinidine 57-24-9, Strychnine 57-27-2, Morphine, biological studies 57-42-1, Meperidine 58-08-2, Caffeine, biological studies 58-15-1, Aminopyrine 58-25-3 58-40-2, Promazine 58-73-1, Diphenhydramine 58-74-2, Papaverine 59-26-7, Nikethamide 59-46-1 60-80-0 60-87-7, Promethazine 60-99-1, Methotrimeprazine 62-44-2, Phenacetin 62-67-9, Nalorphine 68-88-2, Hydroxyzine 68-89-3, Dipyrone 69-23-8, Fluphenazine 69-43-2, Prenylamine lactate 71-82-9, Levallorphan tartrate 72-44-6 72-69-5, Nortriptyline 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-58-4, Ethylmorphine 76-99-3, Methadone 76-99-3D, metabolite 77-07-6, Levorphanol 77-15-6, Ethoheptazine 77-19-0, Dicyclomine 77-37-2 77-39-4, Cycrimine 77-67-8, Ethosuximide 80-77-3, Chlormezanone 82-92-8, Cyclizine 82-98-4, Piperidolate 83-98-7, **Orphenadrine** 84-02-6, Prochlorperazine dimaleate 84-55-9, Viquidil 86-22-6, Brompheniramine 86-75-9, Benzoxiquine 90-39-1, Sparteine 90-54-0, Etafenone 91-79-2, Thenyldiamine 92-12-6, Phenyltoloxamine 92-13-7, Pilocarpine 93-30-1, Methoxyphenamine 96-88-8, Mepivacaine 97-77-8, Disulfiram 99-43-4, Benoxinate 100-92-5, Mephentermine 101-40-6, Propylhexedrine 102-45-4, Cyclopentamine 113-45-1, Methylphenidate 113-59-7, Chlorprothixene 113-92-8, Chlorpheniramine maleate 117-89-5, Trifluoperazine 125-28-0, Dihydrocodeine 127-35-5, Phenazocine 128-62-1, Noscapine 129-03-3, Cyproheptadine 130-95-0 132-20-7, Pheniramine maleate 132-35-4, Proxazole citrate 134-49-6, Phenmetrazine 137-58-6, Lidocaine 144-11-6, Trihexyphenidyl 146-22-5, Nitrazepam 146-48-5, Yohimbine 146-54-3, Triflupromazine 156-08-1 298-46-4, Carbamazepine 298-57-7, Cinnarizine 299-42-3 300-62-9, Amphetamine 303-49-1, Clomipramine 309-29-5, Doxapram 314-35-2, Etamiphyllin 318-23-0, Imolamine 357-57-3, Brucine 359-83-1, Pentazocine 364-62-5, Metoclopramide 372-66-7, Heptaminol 395-28-8, Isoxsuprine 438-60-8 439-14-5, Diazepam 443-48-1, Metronidazole 458-24-2, Fenfluramine 465-65-6, Naloxone 469-62-5, Propoxyphene 479-92-5, Propyphenazone 482-15-5, Isothipendyl 493-92-5, Prolintane 501-68-8, Beclamide 510-53-2, Racemethorphan 511-12-6, Dihydroergotamine 512-15-2, Cyclopentolate 514-65-8, Biperiden 521-78-8, Trimipramine maleate 523-87-5, Dimenhydrinate

524-81-2 525-66-6, Propranolol 526-36-3, Xylometazoline 537-46-2, Methamphetamine 539-15-1, Hordenine 548-73-2, Droperidol 553-06-0 561-27-3, Diacetylmorphine 604-75-1 633-47-6, Cropropamide 634-03-7, Phendimetrazine 642-72-8, Benzydamine 738-70-5, Trimethoprim 749-13-3, Trifluperidol 768-94-5, Amantadine 791-35-5 804-10-4, Chromonar 841-77-0, Norcyclizine 846-49-1 846-50-4, Temazepam 848-75-9, Lormetazepam 852-42-6, Guaiapate 894-76-8, 7-Amino-desmethylflunitrazepam 990-73-8, Fentanyl citrate 1028-33-7, Pentifylline 1088-11-5 1092-46-2, Ketocaine 1165-48-6 1222-57-7, Zolimidine 1420-55-9, Thiethylperazine 1421-14-3, Propanidid 1435-55-8, Hydroquinidine 1617-90-9, Vincamine 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 1668-19-5, Doxepin 1812-30-2, Bromazepam 1893-33-0, Pipamperone 1949-20-8, Oxolamine citrate 2058-52-8, Clothiapine 2167-85-3, Pipazethate 2169-75-7 2180-92-9, Bupivacaine 2558-30-7, Desmethylflunitrazepam 2622-26-6, Pericyazine 2784-55-6 2784-73-8 2886-65-9 2894-67-9, Delorazepam 2898-12-6, Medazepam 2955-38-6, Prazepam 3099-52-3, Nicametate 3572-43-8, Bromhexine 3703-76-2, Cloperastine 3703-79-5, Bamethan 3737-09-5, Disopyramide 3820-67-5, Glafenine 3930-20-9, Sotalol 4093-35-0, Bromopride 4171-13-5, Valnoctamide 4205-90-7, Clonidine 4498-32-2, Dibenzepin 4551-59-1, Fenalamide 4630-95-9, Prifinium bromide 4969-02-2, Methixene 5036-02-2, Tetramisole 5053-06-5, Fenspiride 5118-29-6, Melitracen 5636-83-9, Dimethindene 5741-22-0, Moprolol 6168-76-9, Crotethamide 6452-71-7, Oxprenolol 6493-05-6, Pentoxifylline 6506-37-2, Nimorazole 6724-53-4, Perhexiline maleate 6740-88-1, Ketamine 6856-31-1 7262-75-1, Lefetamine 7456-24-8, Fonazine 10262-69-8, Maprotiline 10418-03-8, Stanozolol 10539-19-2, Moxaverine 11032-41-0, Dihydroergotoxine 13042-18-7, Fendiline 13523-86-9, Pindolol 13669-70-0, Nefopam 14007-64-8, Butethamate 14698-07-8, Tipepidine citrate 14860-49-2, Clobutinol 15301-69-6, Flavoxate 15686-51-8, Clemastine 15687-41-9, Oxyfedrine 17449-96-6, Clofezone 17617-23-1, Flurazepam 17692-51-2, Metergoline 17854-59-0, Mepixanthone 18046-21-4, Fentiazac 18053-31-1, Fominoben 18109-81-4, Butamirate citrate 18683-91-5, Ambroxol 19794-93-5, Trazodone 20448-86-6, Bornaprine 20971-53-3 21363-18-8, Viminol 21829-25-4, Nifedipine 21888-98-2, Dexetimide 22131-35-7, Butalamine 22232-71-9, Mazindol 22316-47-8, Clobazam 22916-47-8, **Miconazole** 23602-78-0, Benfluorex 23779-99-9, Floctafenine 23887-31-2, Clorazepate 24219-97-4, Mianserin 24359-22-6 24526-64-5, Nomifensine 25146-18-3, Febutol 26839-75-8, Timolol 28911-01-5 29769-70-8 29975-16-4, Estazolam
RL: PROC (Process)
(identification of, by principle components anal. of Thin layer chromtog. data and gas chromatog. retention)

L29 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB A reliable and simple method for the routine anal. of pharmaceutical dosage forms by high-performance liq. chromatog. using a C18 Bondapak reversed-phase column with a binary solvent system consisting of MeCN and 0.05M KH2PO4 was developed. Standardized extn. procedures for drugs in various dosage forms were developed and successfully applied to a wide range of current pharmaceutical formulations.

ACCESSION NUMBER: 1987:182729 CAPLUS
DOCUMENT NUMBER: 106:182729
TITLE: General method for the analysis of pharmaceutical dosage forms by high-performance liquid chromatography
AUTHOR(S): Sidhu, A. S.; Kennedy, J. M.; Deeble, S.
CORPORATE SOURCE: Natl. Biol. Stand. Lab., Canberra, Australia

SOURCE: J. Chromatogr. (1987), 391(1), 233-42
CODEN: JOCRAM; ISSN: 0021-9673
DOCUMENT TYPE: Journal
LANGUAGE: English
SO J. Chromatogr. (1987), 391(1), 233-42
CODEN: JOCRAM; ISSN: 0021-9673

IT 50-33-9, Phenylbutazone, analysis 50-34-0, Propantheline bromide
50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine
50-52-2, Thioridazine 50-53-3, Chlorpromazine, analysis 51-48-9,
analysis 51-55-8, Atropine, analysis 52-01-7, Spironolactone
52-53-9, Verapamil 52-86-8, Haloperidol 52-88-0, Atropine methonitrate
53-86-1, Indomethacin 54-05-7, Chloroquine 54-31-9, Frusemide
56-54-2, Quinidine 57-41-0, Phenytoin 57-42-1, Pethidine 57-66-9,
Probenecid 57-68-1, Sulfadimidine 57-96-5, Sulfinpyrazone 58-25-3,
Chlordiazepoxide 58-32-2, Dipyridamole 58-38-8, Prochlorperazine
58-54-8, Ethacrynic acid 58-73-1, Diphenhydramine 58-93-5,
Hydrochlorothiazide 58-94-6, Chlorothiazide 59-63-2, Isocarboxazid
60-87-7, Promethazine 64-86-8, Colchicine 69-23-8, Fluphenazine
72-69-5, Nortriptyline 73-48-3, Bendrofluazide 73-49-4, Quinethazone
76-57-3, Codeine 77-36-1, Chlorthalidone 77-37-2, Procyclidine
83-98-7, **Orphenadrine** 86-22-6 86-34-0, Phensuximide
86-42-0, Amodiaquine 87-00-3, Homatropine 90-34-6, Primaquine
91-75-8, Antazoline 92-13-7, Pilocarpine 94-24-6, Amethocaine
96-88-8 113-92-8, Chlorpheniramine maleate 114-80-7, Neostigmine
bromide 115-79-7, Ambenonium chloride 117-89-5, Trifluoperazine
118-42-3, Hydroxychloroquine 127-69-5, Sulfafurazole 129-03-3,
Cyproheptadine 130-95-0, Quinine 132-17-2, Benztropine mesylate
132-20-7, Pheniramine maleate 135-07-9 137-58-6 144-11-6, Benzhexol
144-80-9, Sulfacetamide 144-82-1, Sulfamethizole 146-22-5, Nitrazepam
147-20-6, Diphenylpyraline 148-79-8, Thiabendazole 298-46-4,
Carbamazepine 315-72-0, Opipramol 364-62-5 396-01-0, Triamterene
438-60-8, Protriptyline 439-14-5, Diazepam 442-52-4, Clemizole
443-48-1, Metronidazole 465-65-6, Naloxone 486-12-4, Triprolidine
500-92-5, Proguanil 514-65-8, Biperiden 521-78-8, Trimipramine maleate
525-66-6, Propranolol 599-79-1, Sulfasalazine 603-50-9, Bisacodyl
604-75-1, Oxazepam 721-50-6, Prilocaine 723-46-6, Sulfamethoxazole
738-70-5, Trimethoprim 742-20-1, Cyclopenthiazide 835-31-4,
Naphazoline 846-49-1, Lorazepam 846-50-4, Temazepam 968-81-0,
Acetohexamide 1131-64-2, Debrisoquine 1134-47-0, Baclofen 1622-61-3,
Clonazepam 1622-62-4, Flunitrazepam 1812-30-2, Bromazepam 2127-01-7,
Clorexolone 2180-92-9, Bupivacaine 2277-92-1 2609-46-3, Amiloride
2898-12-6, Medazepam 2922-44-3, Dextromoramide tartrate 3485-62-9,
Clidinium bromide 3614-69-5, Dimethindene maleate 3902-71-4
3978-86-7, Azatadine maleate 4205-90-7, Clonidine 5543-58-8
6153-33-9 6452-71-7 6893-02-3 7195-27-9, Mefruside 13392-18-2,
Fenoterol 13523-86-9, Pindolol 13655-52-2, Alprenolol 14769-73-4
15180-03-7, Alcuronium chloride 15687-27-1, Ibuprofen 17560-51-9,
Metolazone 17617-23-1, Flurazepam 19216-56-9, Prazosin 21187-98-4,
Gliclazide 21829-25-4, Nifedipine 22204-53-1, Naproxen 22232-54-8,
Carbimazole 22260-51-1, Bromocriptine mesylate 23256-50-0, Guanabenz
acetate 23593-75-1, **Clotrimazole** 24219-97-4 24359-22-6,
Pizotifen maleate 26921-17-5, Timolol maleate 27220-47-9, Econazole
28782-42-5, Difenoxin 32795-47-4, Nomifensine maleate 36894-69-6
38194-50-2, Sulindac 38304-91-5, Minoxidil 42399-41-7, Diltiazem
52365-63-6 53179-11-6 56392-17-7, Metoprolol tartrate 76095-16-4,
Enalapril maleate
RL: ANT (Analyte); ANST (Analytical study)
(HPLC of)

L29 ANSWER 15 OF 24 USPATFULL

AB A transdermal drug delivery system which comprises at least one physiologically active agent or prodrug thereof and at least one dermal penetration enhancer; characterized in that the dermal penetration enhancer is a safe skin-tolerant ester sunscreen. A non-occlusive, percutaneous or transdermal drug delivery system which comprises: (i) an effective amount of at least one physiologically active agent or prodrug thereof; (ii) at least one non-volatile dermal penetration enhancer; and (iii) at least one volatile liquid; characterised in that the dermal penetration enhancer is adapted to transport the physiologically active agent across a dermal surface or mucosal membrane of an animal, including a human, when the volatile liquid evaporates, to form a reservoir or depot of a mixture comprising the penetration enhancer and the physiologically active agent or prodrug within said surface or membrane; and the dermal penetration enhancer is of low toxicity to, and is tolerated by, the dermal surface or mucosal membrane of the animal.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2001:173164 USPATFULL

TITLE: Dermal penetration enhancers and drug delivery systems involving same

INVENTOR(S): Reed, Barry Leonard, Strathmore, Australia
Morgan, Timothy Matthias, Parkville, Australia
Finnin, Barrie Charles, Glen Iris, Australia

PATENT ASSIGNEE(S): Monash University, Victoria, Australia (non-U.S. corporation)

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 6299900	B1	20011009		
	WO 9729735		19970821		<--
APPLICATION INFO.:	US 1998-125436		19981218	(9)	
	WO 1997-AU91		19970219		
			19981218	PCT 371 date	
			19981218	PCT 102(e) date	

	NUMBER	DATE
PRIORITY INFORMATION:	AU 1996-8144	19960219

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Dees, Jose' G.
ASSISTANT EXAMINER: Williamson, Michael A.
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Figure(s); 9 Drawing Page(s)
LINE COUNT: 1675

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 6299900 B1 20011009
WO 9729735 19970821 <--

SUMM Muscle relaxants such as baclofen, diazepam, cyclobenzaprine hydrochloride, dantrolene, methocarbamol, **orphenadrine** and quinine.

SUMM Aminoglycosides such as amikacin, gentamicin, kanamycin, neomycin, netilmicin and tobramycin. Antifungals such as amorolfine, isoconazole, **clotrimazole**, econazole, **miconazole**, nystatin,

terbinafine, bifonazole, amphotericin, griseofulvin, ketoconazole, fluconazole and flucytosine, salicylic acid, fezatione, ticlatone, tolnaftate, triacetin, zinc, pyrithione and sodium pyrithione.

L29 ANSWER 16 OF 24 USPATFULL

AB Compounds having kappa opioid agonist activity, compositions containing them and method of using them as analgesics are provided.

The compounds of formulae I, II, III and IV have the structure: ##STR1## wherein X, X.sub.4, X.sub.5, X.sub.7, X.sub.9 ;

R.sub.1, R.sub.2, R.sub.3, R.sub.4 ; and

Y, Z and n are as described in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 97:107236 USPATFULL

TITLE: Kappa agonist compounds and pharmaceutical formulations thereof

INVENTOR(S): Kruse, Lawrence I., Haddonfield, NJ, United States
Chang, An-Chih, Phoenixville, PA, United States
DeHaven-Hudkins, Diane L., Chester Springs, PA, United States
Farrar, John J., Chester Springs, PA, United States
Gaul, Forrest, Glen Moore, PA, United States
Kumar, Virendra, Paoli, PA, United States
Marella, Michael Anthony, Exton, PA, United States
Maycock, Alan L., Malvern, PA, United States
Zhang, Wei Yuan, Collegeville, PA, United States

PATENT ASSIGNEE(S): Adolor Corporation, Malvern, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5688955		19971118	<--
APPLICATION INFO.:	US 1997-796078		19970205 (8)	

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-612680, filed on 8 Mar 1996

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted

PRIMARY EXAMINER: McKane, Joseph

LEGAL REPRESENTATIVE: Balogh, Imre

NUMBER OF CLAIMS: 15

EXEMPLARY CLAIM: 1

LINE COUNT: 4645

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5688955 19971118 <--

DETD . . . but are not limited to: antibiotics, including cephalosporins, .beta.-lactams, tetracyclines, vancomycins, sulfas and aminoglycosides; antivirals, including acylovir; and antifungals including **clotrimazole**.

DETD . . . analgesics such as aspirin, phenacetin acetaminophen, propoxyphene, pentazocine, codeine, meperidine, oxycodone, mefenamic acid, and ibuprofen; muscle relaxants such as methocarbamol, **orphenadrine**, carisoprodol, meprobamate, chlorphenesin carbamate, diazepam, chlordiazepoxide and chlorzoxazone; analeptics such as caffeine, methylphenidate and pentylenetetrazol; corticosteroids such as methylprednisolone, prednisone,. . .

DETD Imidazoles such as Bifonazole, Butoconazole, Chlordantoin, Chlormidazole, Cloconazole, **Clotrimazole**, Econazole, Enilconazole, Finticonazole, Isoconazole, Ketoconazole, **Miconazole**, Omoconazole, Oxiconazole Nitrate, Sulconazole and Tioconazole;

L29 ANSWER 17 OF 24 USPATFULL

AB A blend of at least two polymers, or at least one polymer and a soluble polyvinylpyrrolidone, in combination with a drug provides a pressure-sensitive adhesive composition for a transdermal drug delivery system in which the drug is delivered from the pressure-sensitive adhesive composition and through dermis when the pressure-sensitive adhesive composition is in contact with human skin. According to the invention, soluble polyvinylpyrrolidone can be used to prevent crystallization of the drug, without affecting the rate of drug delivery from the pressure-sensitive adhesive composition.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	97:70731 USPATFULL	
TITLE:	Solubility parameter based drug delivery system and method for altering drug saturation concentration	
INVENTOR(S):	Miranda, Jesus, Miami, FL, United States Sablotsky, Steven, Miami, FL, United States	
PATENT ASSIGNEE(S):	Noven Pharmaceuticals, Inc., Miami, FL, United States (U.S. corporation)	

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5656286		19970812	<--
APPLICATION INFO.:	US 1994-178558		19940107 (8)	

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1991-722342, filed on 27 Jun 1991, now patented, Pat. No. US 5474783 which is a continuation-in-part of Ser. No. US 1991-671709, filed on 2 Apr 1991, now patented, Pat. No. US 5300291 which is a continuation-in-part of Ser. No. US 1989-295847, filed on 11 Jan 1989, now patented, Pat. No. US 4994267, issued on 19 Feb 1991 which is a continuation-in-part of Ser. No. US 1988-164482, filed on 4 Mar 1988, now patented, Pat. No. US 4814168, issued on 21 Mar 1989

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Venkat, Jyothsna
LEGAL REPRESENTATIVE:	Foley & Lardner
NUMBER OF CLAIMS:	73
EXEMPLARY CLAIM:	1,4
NUMBER OF DRAWINGS:	20 Drawing Figure(s); 19 Drawing Page(s)
LINE COUNT:	3344

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5656286 19970812 <--

DETD Imidazoles such as Bifonazole, Butoconazole, Chlordantoin, Chlormidazole, Cloconazole, **Clotrimazole**, Econazole, Enilconazole, Fenticonazole, Isoconazole, Ketoconazole, **Miconazole**, Omoconazole, Oxiconazole, Nitrate, Sulconazole and Tioconazole;

DETD Aminoalkyl ethers such as Bietanautine, Bromodiphenhydramine, Carbinoxamine, Clemastine, Diphenlypyraline, Doxylamine, Embrammine, Medrylamine, Mephenphydramine, p-Methyldiphenhydramine,

Orphenadrine, Phenyltoloxamine, Piprinhydrinate and Setasine;
DETD 62. Antipsoriatic drugs such as Acitretin, Ammonium Salicylate, Anthralin, 6-Azauridine, **Bergapten**(e), Chrysarobin, Etretinate and Pyrogallol.
DETD . . . Gallamine Triethiodide, Hexacarbacholine Bromide, Hexafluorenium Bromide, Idrocilamide, Lauexium Methyl Sulfate, Leptodactyline, Memantine, Mephenes in, Mephenoxalone, Metaxalone, Methocarbamol, Metocurine Iodide, Nimetazepam, **Orphenadrine**, Pancuronium Bromide, Phenprobamate, Phenyramidol, Pipecurium Bromide, Promoxolane, Quinine Sulfate, Styramate, Succinylcholine Bromide, Succinylcholine Chloride, Succinylcholine Iodine, Suxethonium Bromide, Tetrazepam, Thiocolchicoside,. . .

L29 ANSWER 18 OF 24 USPATFULL
AB Compounds, compositions and method of treating hyperalgesia comprising a compound of formula I, II, III and IV as defined in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	97:59209 USPATFULL			
TITLE:	Kappa agonist compounds and pharmaceutical formulations thereof			
INVENTOR(S):	Kruse, Lawrence I., Haddonfield, NJ, United States Kumar, Virendra, Paoli, PA, United States Chang, An-Chih, Phoenixville, PA, United States DeHaven-Hudkins, Diane L., Chester Springs, PA, United States Farrar, John J., Chester Springs, PA, United States Maycock, Alan L., Malvern, PA, United States			
PATENT ASSIGNEE(S):	Adolor Corporation, Malvern, PA, United States (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5646151		19970708	<--
APPLICATION INFO.:	US 1996-612680		19960308	(8)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	McKane, Joseph			
NUMBER OF CLAIMS:	10			
EXEMPLARY CLAIM:	1			
LINE COUNT:	1630			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5646151 19970708 <--
SUMM . . . but are not limited to: antibiotics, including cephalosporins, .beta.-lactams, tetracyclines, vancomycins, sulfas and aminoglycosides; antivirals, including acylovir; and antifungals including **clotrimazole**.
SUMM . . . analgesics such as aspirin, phenacetin acetaminophen, propoxyphene, pentazocine, codeine, meperidine, oxycodone, mefenamic add, and ibuprofen; muscle relaxants such as methocarbamol, **orphenadrine**, carisoprodol, meprobamate, chlorphenesin carbamate, diazepam, chlordiazepoxide and chlorzoxazone; analeptics such as caffeine, methylphenidate and pentylenetetrazol; corticosteroids such as methylprednisolone, prednisone,. . .
SUMM Imidazoles such as Bifonazole, Butoconazole, Chlordantoin, Chlormidazole, Cloconazole, **Clotrimazole**, Econazole, Enilconazole, Finticonazole, Isoconazole, Ketoconazole, **Miconazole**, Omoconazole, Oxiconazole Nitrate, Sulconazole and

Tioconazole;

L29 ANSWER 19 OF 24 USPATFULL

AB The present invention relates to pharmaceutical compositions for topical application comprising a safe and effective amount of a pharmaceutical active, from about 0.1% to about 10.0% of a high molecular weight cationic polymer, from about 0.05% to about 5% of a high HLB non-ionic surfactant, and from about 0.1% to about 25% of an alkoxylated ether. In further embodiments, these compositions also comprise from about 0.01% to about 5% of a low HLB non-ionic surfactant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	97:24701 USPATFULL
TITLE:	Compositions for topical delivery of drugs comprising a mixture of high and low HLB surfactants and alkoxylated ether
INVENTOR(S):	Bloom, Roberta C., Huntington, CT, United States Deckner, George E., Cincinnati, OH, United States
PATENT ASSIGNEE(S):	The Procter & Gamble Company, Cincinnati, OH, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5614178		19970325	<--
APPLICATION INFO.:	US 1994-265975		19940627 (8)	
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1993-79977, filed on 25 Jun 1993, now abandoned which is a continuation-in-part of Ser. No. US 1993-33211, filed on 18 Mar 1993, now abandoned which is a continuation of Ser. No. US 1992-950527, filed on 25 Sep 1992, now abandoned which is a continuation-in-part of Ser. No. US 1992-920937, filed on 28 Jul 1992, now abandoned			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Kulkosky, Peter F.			
LEGAL REPRESENTATIVE:	Sabatelli, Anthony D., Dabbiere, David K.			
NUMBER OF CLAIMS:	45			
EXEMPLARY CLAIM:	1			
LINE COUNT:	1451			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5614178 19970325 <--

SUMM . . . chlorhexidine, chlortetracycline, oxytetracycline, clindamycin, ethambutol, hexamidine isethionate, metronidazole, pentamidine, gentamicin, kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, **miconazole** and amanfadine. Antimicrobial drugs preferred for inclusion in compositions of the present invention include tetracycline hydrochloride, erythromycin estolate, erythromycin stearate. . . lineomycin hydrochloride, methacycline hydrochloride, methenamine hippurate, methenamine mandelate, minocycline hydrochloride, neomycin sulfate, netilmicin sulfate, paromomycin sulfate, streptomycin sulfate, tobramycin sulfate, **miconazole** hydrochloride, amanfadine hydrochloride, amanfadine sulfate, triclosan, octopirox, parachlorometa xylenol, nystatin, tolnaftate and **clotrimazole**.

SUMM . . . drugs. Muscle relaxant drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of cinnamedrine, cyclobenzaprine, flavoxate, **orphenadrine**, papaverine, mebeverine, idaverine, ritodrine,

dephenoxylate, dantrolene and azumolene.

CLM What is claimed is:

. . . doxycycline, capreomycin, chlorhexidine, chlortetracycline, oxytetracycline, clindamycin, ethambutol, metronidazole, pentamidine, gentamicin, kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, **miconazole** and amanfadine, pharmaceutically-acceptable salts thereof and mixtures thereof.

L29 ANSWER 20 OF 24 USPATFULL

AB An oral pharmaceutical composition comprising a hydrophobic resin or ion exchange resin which has a therapeutic agent bound thereto forming an agent-resin complex is disclosed. The complex is coated with a water-permeable diffusion barrier of poly(vinyl alcohol) polymer cryogel.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	94:15529 USPATFULL
TITLE:	Cryogel oral pharmaceutical composition containing therapeutic agent
INVENTOR(S):	Wood, Louis L., Rockville, MD, United States Calton, Gary J., Elkridge, MD, United States
PATENT ASSIGNEE(S):	SRCHEM Incorporated, Elkridge, MD, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5288503		19940222	<--
APPLICATION INFO.:	US 1992-899369		19920616 (7)	
RELATED APPLN. INFO.:	Division of Ser. No. US 1992-821627, filed on 16 Jan 1992, now patented, Pat. No. US 5260066			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Phelan, Gabrielle			
LEGAL REPRESENTATIVE:	Ramsey, William S.			
NUMBER OF CLAIMS:	5			
EXEMPLARY CLAIM:	1			
LINE COUNT:	1265			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5288503 19940222 <--

SUMM . . . ethanol, isopropanol, formalin, cresol, dimazole, siccanin, phenyliodoundecynoate, hexachlorophene, resorcin, benzethonin chloride, sodium lauryl sulfate, mercuric chloride, meclocycline, mercurochrome, chlorhexidine gluconate, alkyl-polyaminoethylglycine hydrochloride, benzalkonium chloride, nitrofurazone, nystatin, acesulfamin, **clotrimazole**, sulfamethizole, tolnaftate, pentamycin, amphotericin B, pyrrolnitrin, undecylenic acid, **miconazole**, trichomycin, variotin, haloprogin, and dimazole;
Antiviral Agents including:
idoxuridine, trifluridine, vidarabine, DDCI, acyclovir, gancyclovir, pyrimethamine, trisulfapyrimidine, flucytosine, AZT;
Steroidal Anti-inflammatory including:

cortisone, hydrocortisone, prednisolone, prednisone, dexamethasone, fluocinolone, fluorinated-corticoids Nonsteroidal. . .

CLM What is claimed is:

. . . hexachlorophene, resorcin,, benzethonin chloride, sodium lauryl sulfate, mercuric chloride, meclocycline, mercurochrome, chlorhexidine gluconate, alkylpolyaminoethylglycine hydrochloride, benzalkonium chloride, nitrofurazone, nystatin, acesulfamin, **clotrimazole**, sulfamethizole, tolnaftate, pentamycin, amphotericin B, pyrrolnitrin, undecylenic acid, **miconazole**, trichomycin, variotin, haloprogin, and dimazole hydrochloride, idoxuridine, trifluridine, vidarabine, DDCl, acyclovir, gancyclovir, pyrimethamine, trisulfapyrimidine, flucytosine, AZT, fentanyl, cortisone, hydrocortisone, prednisolone,. . . hydrocodone, hydroxychloroquine, hydroxyzine, hyoscyamine, imipramine, levoproproxyphene, maprotiline, meclinzine, mepenzolate, meperidine, mephentermine, mesoridazine, methadone, methdilazine, methscopolamine, methysergide, metoprolol, nortryptiline, noscapine, nylindrin, **orphenadrine**, papaverine, pentazocine, phendimetrazine, phentermine, phenylpropanolamine, pyrilamine, tripelennamine, triprolidine, promazine, propoxyphene, propanolol, pseudoephedrine, pyrilamine, quinidine, scopolamine, propranolol, atenolol, bunitrolol, dextromethorphan, aminocaproic. . .

L29 ANSWER 21 OF 24 USPATFULL

AB An oral sustained release composition for slightly soluble pharmaceutically active agents comprising a core, a wall around said core, and a bore through said wall connecting said core and the environment outside of said wall; wherein said core comprises a slightly soluble active agent, optionally a crystal habit modifier, at least two osmotic driving agents, at least two different (or two different grades of) hydroxyalkyl celluloses, and optionally lubricants, wetting agents, and carriers; said wall being substantially impermeable to said core components and permeable to water and gastro-intestinal fluids. The composition is most especially adapted for administering carbamazepine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	94:11234 USPATFULL
TITLE:	Oral osmotic system for slightly soluble active agents
INVENTOR(S):	Koparkar, Arun D., Westfield, NJ, United States Shah, Shailesh B., Union, NJ, United States
PATENT ASSIGNEE(S):	Ciba-Geigy Corp., Ardsley, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5284662		19940208	<--
APPLICATION INFO.:	US 1991-809026		19911216 (7)	
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1990-590880, filed on 1 Oct 1990, now abandoned			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Page, Thurman K.			
ASSISTANT EXAMINER:	Horne, Leon R.			
LEGAL REPRESENTATIVE:	Fishman, Irving M., Kaiser, Karen G., Ikeler, Barbara J.			
NUMBER OF CLAIMS:	23			
EXEMPLARY CLAIM:	1			
LINE COUNT:	547			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5284662 19940208 <--
DETD . . . oxcarbamazepine, phenytoin, phenobarbital; sedative-hypnotic agents such as triazolam, chlordiazepoxide, temazepam, chlorazepate, alprazolam, diazepam, flurazepam, lorazepam, oxazepam, hydroxyzine, prazepam, meprobamate, butalbital, **orphenadrine**, chlorzoxazone, cyclobenzaprine; antiparkinson agents such as benztropine, carbidopa, levodopa, L 647,339; analgesics such as acetaminophen, oxycodone, hydrocodone, codeine, propoxyphen. Respiratory. . . antiparasitic, and antifungal agents such as cefoxitin, thiabendazole, cephalexin, tetracycline, ampicillin, amoxicillin, sulfamethoxazole, cefaclor, erythromycin, penicillin, nitrofurantoin, minocycline, doxycycline, cefadroxil, **miconazole** , phenazopyridine, norfloxacin, clorsulon, fludalanine, pentizidone, cilastin, phosphonomycin, ivermectin, imipenem, arprinocid, and foscarnet; nutritional supplements including vitamins such as isotretinoin (Vit.. . .

L29 ANSWER 22 OF 24 USPATFULL
AB An article for controlled delivery of an active substance into an aqueous phase has a first layer containing an active substance, and a second layer of a crystalline polymer matrix and a non-ionic surface active agent, the second layer also containing the same or different active substance substantially homogeneously dispersed therein. The article enables release of a drug at a constant plateau level, followed by a pulse of drug after a predetermined time, thus making the composition of the invention especially suitable for use in, e.g., treatment of rheumatoid arthritis or related disorders with non-steroidal anti-inflammatory agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 93:41827 USPATFULL
TITLE: Controlled release article with pulsatile release
INVENTOR(S): Bar-Shalom, Daniel, Kokkedal, Denmark
Kindt-Larsen, Vedbaek, Denmark
PATENT ASSIGNEE(S): Buhk Meditec A/A, Hellerup, Denmark (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5213808		19930525	<--
APPLICATION INFO.:	US 1990-505924		19900406	(7)

	NUMBER	DATE
PRIORITY INFORMATION:	DK 1989-4699	19890922

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Page, Thurman K.
ASSISTANT EXAMINER: Phelan, D. Gabrielle
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1683
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5213808 19930525 <--
SUMM . . . lofepramin, amitriptylin, nortriptylin, protriptylin,

maptrotilin, coffein, cinnarizine, cyclizine, dimenhydinate, meclozine, prometazine, thiethylperazine, metoclopramide, scopolamine, phenobarbital, phenytoine, ethosuximide, primidone, carbamazepine, chlonazepam, **orphenadrine**, atropine, bensatropine, biperiden, metixene, procylidine, levodopa, bromocriptin, amantadine, ambenon, pyridostigmine, synstigmine, disulfiram, morphine, codeine, pentazocine, buprenorphine, pethidine, phenoperidine phentanyl, methadone,. . . sodiummaurothiomalate, auronofin, penicillamine, estradiol, estradiolvalerianate, estriol, ethinylestradiol, dihydrogesteron, lynestrenol, medroxiprogresterone, noretisterone, cyclophenile, clomiphene, levonorgestrel, mestranol, ornidazol, tinidazol, ekonazol, chlotrimazol, natamycine, **miconazole**, sulbentin, methylergotamine, dinoprost, dinoproston, gemeprost, bromocriptine, phenylpropanolamine, sodiumchromoglicate, azetazolamide, dichlophenamide, betacarotene, naloxone, calciumfolinate, in particular clonidine, theophylline, dipyradamol, hydrochlorthiazide, scopolamine,. . .

SUMM . . . the delivery of antimicrobial agents to the vagina. Examples of such agents are antifungals, for example imidazole antifungals such as **clotrimazole**, econazol, ketoconazole and **miconazole**, polyene antifungal antibiotics such as nystatin, and antiprotozoals such as metronidazole and ornidazole.

L29 ANSWER 23 OF 24 USPATFULL

AB Drug delivery compositions yeild new and unexpected degrees of stabilization, solubilization and delivery of incorporated medicaments, drugs, or other physiologically-active compounds. The compositions enable administration of drugs and other medically useful compounds via a variety of routes. More particularly, a drug delivery system or composition including one or more monomeric or polymerized surface active agents allows for rapid dissolution and smooth liberation of any desired incorporated drug or combinations, and the method of preparing the drug composition. In one embodiment, the physiologically-active compound is encapsulated by a coacervate-derived film, and the finished product is suitable for transmucosal administration. Other formulations of this invention may be administered via inhalation, oral, parenteral and by transdermal and transmucosal routes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	90:79697 USPATFULL			
TITLE:	Drug delivery compositions and methods			
INVENTOR(S):	Ecanow, Bernard, Wilmette, IL, United States			
PATENT ASSIGNEE(S):	Medaphore, Inc., Wilmette, IL, United States (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4963367		19901016	<--
APPLICATION INFO.:	US 1987-130550		19871215 (7)	
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1985-711066, filed on 12 Mar 1985, now abandoned And Ser. No. US 1985-710048, filed on 11 Mar 1985, now abandoned And Ser. No. US 1986-835550, filed on 3 Mar 1986, now patented, Pat. No. US 4849405 And Ser. No. US 1986-896844, filed on 14 Aug 1986, now abandoned And Ser. No. US 1987-1314, filed on 8 Jan 1987, now patented, Pat. No. US 4794000 And Ser. No. US 1987-31237, filed on 26 Mar 1987, now patented, Pat.			

No. US 4914084 And Ser. No. US 1987-54193, filed on 26 May 1987, now abandoned And Ser. No. US 1987-54194, filed on 26 May 1987, now abandoned And Ser. No. US 1985-811675, filed on 20 Dec 1985, now patented, Pat. No. US 4738952 which is a continuation-in-part of Ser. No. US 1984-604476, filed on 27 Apr 1984, now abandoned , said Ser. No. 835550 which is a continuation-in-part of Ser. No. US 1984-604483, filed on 9 May 1984, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Lovering, Richard D.
LEGAL REPRESENTATIVE: Marshall, O'Toole, Gerstein, Murray & Bicknell
NUMBER OF CLAIMS: 45
EXEMPLARY CLAIM: 1,27
LINE COUNT: 2363
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 4963367 19901016 <--
DETD . . . 5.0-7.5

Methiodal Sodium	5.0-8.0
Methocarbamol	3.5-6.0
Methohexital Sodium	10.6-11.6
Methotrexate Sodium	8.0-9.0
Methotrimeprazine	3.0-5.0
Methoxamine HCl	3.0-5.0
Methscopolamine Bromide	4.5-6.0
Methyldopate HCl	3.0-4.2
Methylergonovine Maleate	2.7-3.5
Methylpredisolone Sodium Succinate	7.0-8.0
Metronidazone	4.5-7.0
Miconazole	3.7-5.7
Minocycline HCl	2.0-3.5
Mitomycin	6.0-8.0
Morphine Sulfate	2.5-6.0
Moxalactam Disodium	4.5-7.0
Nafcillin Sodium	6.0-8.5
Naloxone HCl	3.0-4.5
Neostigmine Methylsulfate	5.-6.5
Netilmicin Sulfate	3.5-6.0
Niacin	4.0-6.0
Niacinamide	5.0-7.0
Norepinephrine Bitartrate	3.0-4.5
Nylidrin HCl	4.5-6.5
Orphenadrine Citrate	5.0-6.0
Oxacillin Sodium	5.0-8.5
Oxymorphone HCl	2.7-4.5
Oxytetracycline	8.0-9.0
Oxytetracycline HCl	2.0-3.0
Oxytocin	2.5-4.5
Papaverine HCl	3.0 or less
Parathyroid	2.5-3.5
Penicillin G Potassium	6.5-8.5

Penicillin G Procaine. . .
DETD . . . mg/ml
Fluphenazine HCl 2.5 mg/ml
Heparin Sodium 1,00-20,000 units/ml
Haloperidol lactate 5 mg/ml
Insulin 40 units
Ketamine HCl 10 mg/ml
Labeltol HCl 5 mg/ml
Lipocaine HCl 10 mg/ml
Miconazole 10 mg/ml
Morphine Sulfate 0.5-1.0 mg/ml
Dropendal 2.5 mg/ml
Imipramine HCl 25 mg/2 ml
Phenytoin 100 mg/ml
Pentobartital Sodium 50 mg/ml
Tetracycline HCl 250 mg/100 ml
Thiopental. . .

L29 ANSWER 24 OF 24 USPATFULL
AB The instant invention is directed to a lipid osmotic pump, comprising:

(A) a core, comprising:

(i) a beneficial amount of at least one substantially water insoluble active agent which is lipid soluble and/or lipid wettable;

(ii) a sufficient amount of at least one water immiscible lipid carrier, which is liquid at the temperature of intended use, to dissolve and/or suspend said active agent; and

(iii) a sufficient amount of at least one osmotic agent to ensure release of said lipid carrier from the pump; and

(B) surrounded by a water insoluble wall:

(i) having a thickness of about 1 to 1000 microns;

(ii) which is preferentially wetted by said lipid carrier over an aqueous solution of said osmotic agent;

(iii) having a water permeability of about 1.times.10.sup.-18 to 4.times.10.sup.-15 cm.sup.3 sec/g;

(iv) prepared from at least one polymer permeable to water but substantially impermeable to said osmotic agent; and

(v) having a means for said active agent and lipid carrier to be released through said water insoluble wall.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 87:56611 USPATFULL
TITLE: Lipid osmotic pump
INVENTOR(S): Amidon, Gordon L., Ann Arbor, MI, United States
Higuchi, Takeru, Lawrence, KS, United States
Dressman, Jennifer B., Ann Arbor, MI, United States
PATENT ASSIGNEE(S): Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4685918		19870811	<--
APPLICATION INFO.:	US 1985-697105		19850201 (6)	

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Kight, John
ASSISTANT EXAMINER: Nutter, Nathan
LEGAL REPRESENTATIVE: DiPrima, Joseph F., Olson, R. Brent
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 28 Drawing Figure(s); 25 Drawing Page(s)
LINE COUNT: 1250
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 4685918 19870811 <--

DETD . . . carbamazepine, phenytoin, phenobarbital; sedative-hypnotic agents such as triazolam, chlordiazepoxide, temazepam, chlorazepate, alprazolam, diazepam, flurazepam, lorazepam, oxazepam, hydroxyzine, prazepam, meprobamate, butalbital, **orphenadrine**, chlorzoxazone, cyclobenzaprine; antiparkinson agents such as benztropine, carbidopa, levodopa, L 647,339; analgesics such as acetaminophen, oxycodone, hydrocodone, codeine, propoxyphen. Respiratory. . . antiparasitic, and antifungal agents such as cefoxitin, thiabendazole, cephalexin, tetracycline, ampicillin, amoxicillin, sulfamethoxazole, cefaclor, erythromycin, penicillin, nitrofurantoin, minocycline, doxycycline, cefadroxil, **miconazole** , phenazopyridine, norfloxacin, clorsulon, fludalanine, pentizidone, cilastin, phosphonomycin, ivermectin, imipenem, arprinocid, and foscarnet; nutritional supplements including vitamins such as isotretinoin (Vit.. . .

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=> d his

     (FILE 'HOME' ENTERED AT 17:15:02 ON 10 APR 2002)

     FILE 'REGISTRY' ENTERED AT 17:15:12 ON 10 APR 2002
                E METHOXSALEN/CN
L1             1 S E3

     FILE 'CAPLUS, USPATFULL' ENTERED AT 17:15:41 ON 10 APR 2002
L2          2642 S L1
L3          2782 S (L2 OR METHOXSALEN?)
L4            52 S L3 AND (NICOTINE OR CYP2A6 OR COTININE OR TOBACCO OR SMOKING)
L5            52 DUP REM L4 (0 DUPLICATES REMOVED)
L6            17 S L5 AND PY<=1996
L7             4 S L4 AND CYP2B6
L8             0 S L5 AND PY<=199
L9            28 S L5 AND PY<=1999
L10          489 S ORPHENADRIN?
L11           80 S L10 AND (NICOTINE OR CYP2A6 OR COTININE OR TOBACCO OR SMOKING
L12           80 DUP REM L11 (0 DUPLICATES REMOVED)
L13           57 S L12 AND PY<=1999
L14           22 S CYP2B6(P)(INHIBITOR OR ANTAGONSIT#) AND (NICOTINE OR CYP2A6 O
L15           19 S L14 AND PY <=1999
L16            0 S CYP2B6(P)(INHIBITOR OR ANTAGONIST#) AND (NICOTINE OR TOBACCO
L17           74 S L10 AND (NICOTINE OR COTININE OR TOBACCO OR SMOKING)
L18           51 S L17 AND PY<=1999
L19           42 S L17 AND PY<=1997

     FILE 'STNGUIDE' ENTERED AT 17:49:59 ON 10 APR 2002

     FILE 'CAPLUS, USPATFULL' ENTERED AT 17:54:34 ON 10 APR 2002
L20            2 S L3 AND ORPHENADRIN?
L21            2 DUP REM L20 (0 DUPLICATES REMOVED)
L22           19 S L4 AND PY<=1997
L23           52 S PILOCARPIN? AND ORPHENADRIN?
L24            1 S PILOCARPIN? AND CYP2B6(P)(INHIBITOR# OR ANTAGONIST#)
L25           16 S L23 AND PY<=1997
L26           16 DUP REM L25 (0 DUPLICATES REMOVED)

     FILE 'STNGUIDE' ENTERED AT 18:46:35 ON 10 APR 2002

     FILE 'CAPLUS, USPATFULL' ENTERED AT 19:00:30 ON 10 APR 2002
L27           82 S (MICONAZOL? OR CLOTRIMAZOL? OR AFLATOXIN(2A)B OR COUMARIN? OR
L28           81 DUP REM L27 (1 DUPLICATE REMOVED)
L29           24 S L28 AND PY<=1997
L30           43 S (MICONAZOL? OR CLOTRIMAZOL? OR AFLATOXIN(2A)B OR COUMARIN? OR
L31           14 S L30 AND PY<=1997

     FILE 'STNGUIDE' ENTERED AT 19:18:47 ON 10 APR 2002

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=> s l23 and py<=1997
L25         16 L23 AND PY<=1997

=> dup rem l25
PROCESSING COMPLETED FOR L25
L26          16 DUP REM L25 (0 DUPLICATES REMOVED)

=> d l26 abs ibib kwic 1-16
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pilocarpine & vrp hexadrine

L26 ANSWER 1 OF 16 USPATFULL

AB A transdermal drug delivery system which comprises at least one physiologically active agent or prodrug thereof and at least one dermal penetration enhancer; characterized in that the dermal penetration enhancer is a safe skin-tolerant ester sunscreen. A non-occlusive, percutaneous or transdermal drug delivery system which comprises: (i) an effective amount of at least one physiologically active agent or prodrug thereof; (ii) at least one non-volatile dermal penetration enhancer; and (iii) at least one volatile liquid; characterised in that the dermal penetration enhancer is adapted to transport the physiologically active agent across a dermal surface or mucosal membrane of an animal, including a human, when the volatile liquid evaporates, to form a reservoir or depot of a mixture comprising the penetration enhancer and the physiologically active agent or prodrug within said surface or membrane; and the dermal penetration enhancer is of low toxicity to, and is tolerated by, the dermal surface or mucosal membrane of the animal.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2001:173164 USPATFULL			
TITLE:	Dermal penetration enhancers and drug delivery systems involving same			
INVENTOR(S):	Reed, Barry Leonard, Strathmore, Australia Morgan, Timothy Matthias, Parkville, Australia Finnin, Barrie Charles, Glen Iris, Australia			
PATENT ASSIGNEE(S):	Monash University, Victoria, Australia (non-U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6299900	B1	20011009	
	WO 9729735		19970821	<--
APPLICATION INFO.:	US 1998-125436		19981218	(9)
	WO 1997-AU91		19970219	
			19981218	PCT 371 date
			19981218	PCT 102(e) date
	NUMBER		DATE	
PRIORITY INFORMATION:	AU 1996-8144		19960219	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	GRANTED			
PRIMARY EXAMINER:	Dees, Jose' G.			
ASSISTANT EXAMINER:	Williamson, Michael A.			
LEGAL REPRESENTATIVE:	Foley & Lardner			
NUMBER OF CLAIMS:	25			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	9 Drawing Figure(s); 9 Drawing Page(s)			
LINE COUNT:	1675			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 6299900 B1 20011009
WO 9729735 19970821 <--
SUMM Muscle relaxants such as baclofen, diazepam, cyclobenzaprine hydrochloride, dantrolene, methocarbamol, **orphenadrine** and quinine.
SUMM . . . compounds, preferably sumatriptan; and antihypertensives, preferably clonidine, amlodipine and nitrendipine; and anti-malarials, preferably primaquine; and minoxidil and minoxidil pro-drugs; and **pilocarpine**; and bronchodilators, preferably salbutamol, terbutaline, salmeterol; and anti-depressants, preferably ibogaine, bupropion and rolipram; and anti-alzheimer's agents, preferably fluphenazine and haloperidol;. . .
CLM What is claimed is:
. . . derivatives, melatonin, n-docosanol, tromantadine, lipophilic pro-drugs of acyclovir, low molecular weight heparin, enoxaparin, sumatriptan, amlodipine, nitrendipine, primaquine, minoxidil, minoxidil pro-drugs, **pilocarpine**, salbutamol, terbutaline, salmeterol, ibogaine, bupropian, rolipram, tacrine, fluphenazine, haloperidol, N-0923, cyproterone acetate or mazindol.

L26 ANSWER 2 OF 16 USPATFULL
AB Method and means for delivery of drugs to the optic nerve head and the region surrounding it which comprises contacting the surface of the eye with an effective amount of a drug for treatment of said nerve head and a physiologically acceptable prostaglandin or prostaglandin derivative for enhancing delivery of the drug to the nerve head, in an opththalmologically acceptable carrier.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	1999:110367 USPATFULL			
TITLE:	Methods and means for drug administration			
INVENTOR(S):	Stjernschantz, Johan, Uppsala, Sweden Selen, Goran, Uppsala, Sweden			
PATENT ASSIGNEE(S):	Pharmacia & Upjohn AB, Stockholm, Sweden (non-U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5952378		19990914	
	WO 9605840		19960229	<--
APPLICATION INFO.:	US 1997-793043		19970605	(8)
	WO 1995-SE962		19950824	
			19970605	PCT 371 date
			19970605	PCT 102(e) date
	NUMBER		DATE	
PRIORITY INFORMATION:	SE 1994-2816		19940824	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Fay, Zohreh			
LEGAL REPRESENTATIVE:	Dinsmore & Shohl LLP			
NUMBER OF CLAIMS:	19			
EXEMPLARY CLAIM:	1			
LINE COUNT:	425			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5952378 19990914
WO 9605840 19960229 <--
SUMM Anticholinergic Agents such as Biperiden, Trihexyphenidyl, Metixen, Procyclidine, **Orphenadrine**, Atropine, Benzatropine, Homatropine, Scopolamine, BM-5;
DETD Crawford K, Kaufman P L, and True Gabelt, B'A (1987). **Pilocarpine** antagonizes PGF2.mu.-induced ocular hyptension: Evidence for enhancement of uveoscleral outflow by PGF2.mu.. Invest. Ophthalmol. Vis Sci p. 11.

L26 ANSWER 3 OF 16 USPATFULL
AB Compounds having kappa opioid agonist activity, compositions containing them and method of using them as analgesics are provided.

The compounds of formulae I, II, III and IV have the structure: ##STR1## wherein X, X.sub.4, X.sub.5, X.sub.7, X.sub.9 ;

R.sub.1, R.sub.2, R.sub.3, R.sub.4 ; and

Y, Z and n are as described in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 97:107236 USPATFULL
TITLE: Kappa agonist compounds and pharmaceutical formulations thereof
INVENTOR(S): Kruse, Lawrence I., Haddonfield, NJ, United States
Chang, An-Chih, Phoenixville, PA, United States
DeHaven-Hudkins, Diane L., Chester Springs, PA, United States
Farrar, John J., Chester Springs, PA, United States
Gaul, Forrest, Glen Moore, PA, United States
Kumar, Virendra, Paoli, PA, United States
Marella, Michael Anthony, Exton, PA, United States
Maycock, Alan L., Malvern, PA, United States
Zhang, Wei Yuan, Collegeville, PA, United States
PATENT ASSIGNEE(S): Adolor Corporation, Malvern, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5688955		19971118	<--
APPLICATION INFO.:	US 1997-796078		19970205	(8)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1996-612680, filed on 8 Mar 1996			
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	McKane, Joseph			
LEGAL REPRESENTATIVE:	Balogh, Imre			
NUMBER OF CLAIMS:	15			
EXEMPLARY CLAIM:	1			
LINE COUNT:	4645			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5688955 19971118 <--
DETD . . . analgesics such as aspirin, phenacetin acetaminophen, propoxyphene, pentazocine, codeine, meperidine, oxycodone, mefenamic acid, and ibuprofen; muscle relaxants such as methocarbamol, **orphenadrine**, carisoprodol, meprobamate, chlorphenesin carbamate, diazepam, chlordiazepoxide and chlorzoxazone; analeptics such

as caffeine, methylphenidate and pentylenetetrazol; corticosteroids such as methylprednisolone, prednisone,. . .
DETD Antiglaucoma agents, such as Dapiprazoke, Dichlorphenamide, Dipivefrin and **Pilocarpine**.

L26 ANSWER 4 OF 16 USPATFULL
AB A blend of at least two polymers, or at least one polymer and a soluble polyvinylpyrrolidone, in combination with a drug provides a pressure-sensitive adhesive composition for a transdermal drug delivery system in which the drug is delivered from the pressure-sensitive adhesive composition and through dermis when the pressure-sensitive adhesive composition is in contact with human skin. According to the invention, soluble polyvinylpyrrolidone can be used to prevent crystallization of the drug, without affecting the rate of drug delivery from the pressure-sensitive adhesive composition.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 97:70731 USPATFULL
TITLE: Solubility parameter based drug delivery system and method for altering drug saturation concentration
INVENTOR(S): Miranda, Jesus, Miami, FL, United States
Sablotsky, Steven, Miami, FL, United States
PATENT ASSIGNEE(S): Noven Pharmaceuticals, Inc., Miami, FL, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5656286		19970812	<--
APPLICATION INFO.:	US 1994-178558		19940107 (8)	

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1991-722342, filed on 27 Jun 1991, now patented, Pat. No. US 5474783 which is a continuation-in-part of Ser. No. US 1991-671709, filed on 2 Apr 1991, now patented, Pat. No. US 5300291 which is a continuation-in-part of Ser. No. US 1989-295847, filed on 11 Jan 1989, now patented, Pat. No. US 4994267, issued on 19 Feb 1991 which is a continuation-in-part of Ser. No. US 1988-164482, filed on 4 Mar 1988, now patented, Pat. No. US 4814168, issued on 21 Mar 1989
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Venkat, Jyothsna
LEGAL REPRESENTATIVE: Foley & Lardner
NUMBER OF CLAIMS: 73
EXEMPLARY CLAIM: 1,4
NUMBER OF DRAWINGS: 20 Drawing Figure(s); 19 Drawing Page(s)
LINE COUNT: 3344
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5656286 19970812 <--
SUMM . . . albuterol, or a cardioactive agent, such as nitroglycerin. In still other embodiments, the drug is a cholinergic agent, such as **pilocarpine**, or an antipsychotic such as haloperidol or a tranquilizer/sedative such as alprazolam.
DRWD FIG. 10 is a graphical representation of steady-state flux of **pilocarpine** through cadaver skin in vitro from the drug delivery systems of the prior art, specifically single polymeric adhesives of silicone. . .
DETD . . . Parameter

Components	(J/cm.sup.3).sup.1/2
ethylene/vinyl acetate (404 VAc)	20.9
polydimethylsiloxane	15.1
polyisobutylene	17.6
polyethylene	17.6
polyethyl methacrylate	19.8
polyethyl acrylate	20.9
polymethyl acrylate	21.7
polymethyl methacrylate	22.3
polystyrene	22.5
nitroglycerin	27.0
estradiol	24.5
norethindrone acetate	21.3
pilocarpine	22.9
albuterol	26.7

DETD 38. Antiglaucoma drugs such as Acetazolamide, Befunolol, Betaxolol, Bupranolol, Carteolol, Dapiprazoke, Dichlorphenamide, Dipivefrin, Epinephrine, Levobunolol, Methazolamide, Metipranolol, **Pilocarpine**, Pindolol and Timolol.

DETD Aminoalkyl ethers such as Bietanautine, Bromodiphenhydramine, Carbinoxamine, Clemastine, Diphenlypyraline, Doxylamine, Embrammine, Medrylamine, Mephenphydramine, p-Methyldiphenhydramine, **Orphenadrine**, Phenyltoloxamine, Piprinhydrinate and Setasine;

DETD 116. Miotic drugs such as Carbachol, Physostigmine, **Pilocarpine** and Pilocarpus.

DETD . . . Gallamine Triethiodide, Hexacarbacholine Bromide, Hexafluorenium Bromide, Idrocilamide, Lauexium Methyl Sulfate, Leptodactyline, Memantine, Mephenes in, Mephenoxalone, Metaxalone, Methocarbamol, Metocurine Iodide, Nimetazepam, **Orphenadrine**, Pancuronium Bromide, Phenprobamate, Phenyramidol, Pipecurium Bromide, Promoxolane, Quinine Sulfate, Styramate, Succinylcholine Bromide, Succinylcholine Chloride, Succinylcholine Iodine, Suxethonium Bromide, Tetrazepam, Thiocolchicoside,. . .

DETD . . . adhesives (polysiloxanes) in organic solutions. BIO-PSA-3027 is particularly suitable for use in formulations containing aminefunctional drugs, such as albuterol and **pilocarpine**, in the following examples.

DETD A **pilocarpine**-polymer mixture was prepared by combining 5.0 parts of **pilocarpine** base, 1.2 parts of lecithin, 0.8 parts of propylene glycol, 2.0 parts of oleic acid, 2.5 parts of silicone fluid. . . Fluid, 100 cs), and 77.0 parts of polysiloxane (BIO-PSA X7-3027), and mixing well in an appropriate container. Example 22 incorporated **pilocarpine** into a polyacrylate comprising National Starch Acrylic Adhesive, Duro-Tak 80-1196. Example 23 employed a blend of polysiloxane and polyacrylate in. . .

DETD TABLE X

Ingredient	21	22	23

Polyacrylate	--	82.0	41.0
Polysiloxane	77.0	--	41.0
Silicone fluid	5.0	--	--
Pilocarpine	10.0	10.0	10.0
Oleic acid	4.0	4.0	4.0
Propylene glycol	1.6	1.6	1.6
Lecithin fluid	2.4	2.4	2.4

DETD **Pilocarpine** flux in vitro from the systems of Examples 21, 22, and 23 is shown in FIG. 10. As seen in. . . invention. In this embodiment of the invention, the combination of polyacrylate and polysiloxane polymers adjusted the delivery of rate of **pilocarpine** within the ranges established by single polymer compositions.

DETD

. . . 41.0											
Polychloroprene (19.2)								41.0			
Polyacrylonitrile (26.0)									20.0		
Butadiene/acrylonitrile (18.9)										20.0	
Nitroglycerine (27)	20.8										
		20.8									
17.beta.-estradiol (24.5)			2.0	2.0	2.0	2.0					
Norethindrone acetate (21.3)			2.0	2.0	3.0	3.0					
Pilocarpine (22.9)								10.0			
								10.0			
Albuterol (26.7)									20.0	20.0	
Oleic acid	2.0	2.0	5.0	5.0	2.0	2.0		4.0	4.0	8.0	8.0
Propylene glycol	0.8	0.8.	.	.							

DETD

EXAMPLE 68

COMPONENT	PERCENT BY WEIGHT
Polysiloxane Adhesive (BIO-PSA X7-4301)	54.00
Styrene-ethylene/butylene-styrene polymer (Kraton G1657)	20.00
Lecithin	3.00
Oleic Acid	5.00
Tocopherol Acetate (Vitamin E Acetate)	3.00
Pilocarpine	15.00
	100.00

CLM What is claimed is:

. . . system of claim 35, wherein said cholinergic agonist is selected from the group consisting of choline, acetylcholine, methacholine, carbachol,

bethanechol, **pilocarpine**, muscarine and arecoline.

37. The transdermal drug delivery system of claim 36, wherein said cholinergic agohist is **pilocarpine**, and wherein said **pilocarpine** is present in said system in an amount of less than about 30% by weight.

L26 ANSWER 5 OF 16 USPATFULL

AB Compounds, compositions and method of treating hyperalgesia comprising a compound of formula I, II, III and IV as defined in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	97:59209 USPATFULL	
TITLE:	Kappa agonist compounds and pharmaceutical formulations thereof	
INVENTOR(S):	Kruse, Lawrence I., Haddonfield, NJ, United States Kumar, Virendra, Paoli, PA, United States Chang, An-Chih, Phoenixville, PA, United States DeHaven-Hudkins, Diane L., Chester Springs, PA, United States Farrar, John J., Chester Springs, PA, United States Maycock, Alan L., Malvern, PA, United States	
PATENT ASSIGNEE(S):	Adolor Corporation, Malvern, PA, United States (U.S. corporation)	

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 5646151		19970708		<--
APPLICATION INFO.:	US 1996-612680		19960308	(8)	
DOCUMENT TYPE:	Utility				
FILE SEGMENT:	Granted				
PRIMARY EXAMINER:	McKane, Joseph				
NUMBER OF CLAIMS:	10				
EXEMPLARY CLAIM:	1				
LINE COUNT:	1630				

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 5646151 19970708 <--

SUMM . . . analgesics such as aspirin, phenacetin acetaminophen, propoxyphene, pentazocine, codeine, meperidine, oxycodone, mefenamic add, and ibuprofen; muscle relaxants such as methocarbamol, **orphenadrine**, carisoprodol, meprobamate, chlorphenesin carbamate, diazepam, chlordiazepoxide and chlorzoxazone; analeptics such as caffeine, methylphenidate and pentylenetetrazol; corticosteroids such as methylprednisolone, prednisone,. . .

SUMM Antiglaucoma agents, such as Dapiprazoke, Dichlorphenamide, Dipivefrin and **Pilocarpine**.

L26 ANSWER 6 OF 16 USPATFULL

AB An efficient transdermal delivery system for delivering an active ingredient to the blood supply of a living body, comprising a vasodilator and/or topical counter irritant, an active ingredient, a permeation enhancer for the active ingredient, and a water soluble gum for binding the foregoing. A non-breathable layer also can be used for controlling the microenvironment at the transport site. Compression can be used to further enhance the blood supply at the transport site.

ACCESSION NUMBER: 97:58919 USPATFULL

TITLE: Molecular transdermal transport system
INVENTOR(S): Masiz, John J., 26 High St., Topsfield, MA, United States 01983

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5645854		19970708	<--
APPLICATION INFO.:	US 1995-542068		19951012 (8)	

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-227365, filed on 13 Apr 1994, now patented, Pat. No. US 5460821 which is a continuation-in-part of Ser. No. US 1993-81567, filed on 23 Jun 1993, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Phelan, Gabrielle
LEGAL REPRESENTATIVE: Nields & Lemack
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
LINE COUNT: 425
PI US 5645854 19970708 <--
DETD . . . nafcillin, nalidixic acid, naproxen, narcotic analgesics, neomycin, neostigmine, niacin, nicotine, nifedipine, nitrates, nitrofurantoin, nomifensine, norethindrone, norethindrone acetate, norgestrel, nylidrin, nystatin, **orphenadrine**, oxacillin, oxazepam, oxprenolol, oxymetazoline, oxyphenbutazone, pancrelipase, pantothenic acid, papaverine, para-aminosalicylic acid, paramethasone, paregoric, pemoline, penicillamine, penicillin, penicillin-v, pentobarbital, perphenazine, phenacetin, phenazopyridine, pheniramine, phenobarbital, phenolphthalein, phenprocoumon, phensuximide, phenylbutazone, phenylephrine, phenylpropanolamine, phenyl toloxamine, phenytoin, **pilocarpine**, pindolol, piper acetazine, piroxicam, poloxamer, polycarbophil calcium, polythiazide, potassium supplements, pruzepam, prazosin, prednisolone, prednisone, primidone, probenecid, probucol, procainamide, procarbazine, prochlorperazine,. . .

L26 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2002 ACS
AB Comparison of 7-hydroxylation of coumarin, a CYP2A6 substrate, in human and African green and cynomolgus monkey liver microsomes was made by an HPLC assay with UV detection. In human liver microsomes, the Km and Vmax values for the metabolic conversion were 2.1 .mu.M and 0.79 nmol/mg/min, resp. While African green monkey showed Km and Vmax values of 2.7 .mu.M and 0.52 nmol/mg/min, which were similar to human, higher Km and Vmax values were found in cynomolgus monkey. Coumarin 7-hydroxylation in human and African green monkey was selectively inhibited by methoxsalen and **pilocarpine** (CYP2A6 inhibitors) but not by other inhibitors, i.e. .alpha.-naphthoflavone (CYP1A1), **orphenadrine** (CYP2B6), sulfaphenazole (CYP2C9), quinidine (CYP2D6), and ketoconazole (CYP3A4). Immunoinhibition results supported CYP2A6 involvement in human and its homolog in monkey in coumarin 7-hydroxylation, as only anti-CYP2A6, but not CYP2B1, CYP2C13, CYP2D6, CYP2E1, or CYP3A antibodies, inhibited this conversion. African green monkey was similar to human in catalytic activity of coumarin 7-hydroxylation and response to CYP2A6 inhibitors or antibody inhibition. However, the monkey CYP2A6 is not identical to the human in that Ki values were different, and differences were obsd. with some CYP2A6 inhibitors, such as nicotine and methoxsalen, suggesting that, under some circumstances, studies of nicotine kinetics and drug taking behavior in monkey may not be comparable to human.
ACCESSION NUMBER: 1998:150136 CAPLUS

DOCUMENT NUMBER: 128:164257
TITLE: Comparison of CYP2A6 catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes
AUTHOR(S): Li, Yan; Li, Ning Yuan; Sellers, Edward M.
CORPORATE SOURCE: Dep. Pharmacology, Medicine, Psychiatry, Univ. Toronto, Toronto, ON, M5S 1A8, Can.
SOURCE: Eur. J. Drug Metab. Pharmacokinet. (1997), 22(4), 295-304
CODEN: EJDPD2; ISSN: 0378-7966
PUBLISHER: Medecine et Hygiene
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Eur. J. Drug Metab. Pharmacokinet. (1997), 22(4), 295-304
CODEN: EJDPD2; ISSN: 0378-7966

AB Comparison of 7-hydroxylation of coumarin, a CYP2A6 substrate, in human and African green and cynomolgus monkey liver microsomes was made by an HPLC assay with UV detection. In human liver microsomes, the Km and Vmax values for the metabolic conversion were 2.1 .mu.M and 0.79 nmol/mg/min, resp. While African green monkey showed Km and Vmax values of 2.7 .mu.M and 0.52 nmol/mg/min, which were similar to human, higher Km and Vmax values were found in cynomolgus monkey. Coumarin 7-hydroxylation in human and African green monkey was selectively inhibited by methoxsalen and **pilocarpine** (CYP2A6 inhibitors) but not by other inhibitors, i.e. .alpha.-naphthoflavone (CYP1A1), **orphenadrine** (CYP2B6), sulfaphenazole (CYP2C9), quinidine (CYP2D6), and ketoconazole (CYP3A4). Immunoinhibition results supported CYP2A6 involvement in human and its homolog in monkey in coumarin 7-hydroxylation, as only anti-CYP2A6, but not CYP2B1, CYP2C13, CYP2D6, CYP2E1, or CYP3A antibodies, inhibited this conversion. African green monkey was similar to human in catalytic activity of coumarin 7-hydroxylation and response to CYP2A6 inhibitors or antibody inhibition. However, the monkey CYP2A6 is not identical to the human in that Ki values were different, and differences were obsd. with some CYP2A6 inhibitors, such as nicotine and methoxsalen, suggesting that, under some circumstances, studies of nicotine kinetics and drug taking behavior in monkey may not be comparable to human.

IT 92-13-7, **Pilocarpine** 298-81-7, Methoxsalen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(selective inhibition of coumarin 7-hydroxylation by)

L26 ANSWER 8 OF 16 USPATFULL

AB An efficient transdermal delivery system for delivering an active ingredient to the blood supply of a living body, comprising a vasodilator and/or topical counter irritant, an active ingredient, a permeation enhancer for the active ingredient, and a water soluble gum for binding the foregoing. A non-breathable layer also can be used for controlling the microenvironment at the transport site. Compression can be used to further enhance the blood supply at the transport site.

ACCESSION NUMBER: 95:94689 USPATFULL
TITLE: Molecular transdermal transport system
INVENTOR(S): Masiz, John J., 26 High St., Topsfield, MA, United States 01983

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5460821		19951024	<--
APPLICATION INFO.:	US 1994-227365		19940413	(8)

09/214,851

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1993-81567, filed on 23 Jun 1993, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Phelan, D. Gabrielle
LEGAL REPRESENTATIVE: Nields & Lemack
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
LINE COUNT: 379
PI US 5460821 19951024 <--
SUMM . . . nafcillin, nalidixic acid, naproxen, narcotic analgesics, neomycin, neostigmine, niacin, nicotine, nifedipine, nitrates, nitrofurantoin, nomifensine, norethindrone, norethindrone acetate, norgestrel, nylidrin, nystatin, **orphenadrine**, oxacillin, oxazepam, oxprenolol, oxymetazoline, oxyphenbutazone, pancrelipase, pantothenic acid, papaverine, para-aminosalicylic acid, paramethasone, paregoric, pemoline, penicillamine, penicillin, penicillin-v, pentobarbital, perphenazine, phenacetin, phenazopyridine, pheniramine, phenobarbital, phenolphthalein, phenprocoumon, phensuximide, phenylbutazone, phenylephrine, phenylpropanolamine, phenyl toloxamine, phenytoin, **pilocarpine**, pindolol, piper acetazine, piroxicum, poloxamer, polycarbophil calcium, polythiazide, potassium supplements, pruzepam, prazosin, prednisolone, prednisone, primidone, probenecid, probucol, procainamide, procarbazine, prochlorperazine,. . .

L26 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2002 ACS
AB Capillary zone electrophoresis (CZE) is shown to be capable of detecting a large no. of basic drugs at concns. considered to be forensically significant. A procedure for prepg. exts. of whole blood for anal. by CZE is presented. Relative migration times are presented for over 400 drugs, analyzed using 100 mmol/L phosphate run buffer of pH 2.5 and pH 9.5.
ACCESSION NUMBER: 1995:729623 CAPLUS
DOCUMENT NUMBER: 123:190633
TITLE: Capillary zone electrophoresis in a comprehensive screen for basic drugs in whole blood
AUTHOR(S): Hudson, J.C.; Golin, M.; Malcolm, M.
CORPORATE SOURCE: Toxicology Section, RCMP Forensic Laboratory, Regina, SK, S4P 3J7, Can.
SOURCE: J. - Can. Soc. Forensic Sci. (**1995**), Volume Date 1995, 28(2), 137-52
CODEN: JCFSBP; ISSN: 0008-5030
DOCUMENT TYPE: Journal
LANGUAGE: English
SO J. - Can. Soc. Forensic Sci. (**1995**), Volume Date 1995, 28(2), 137-52
CODEN: JCFSBP; ISSN: 0008-5030
IT 50-36-2, Cocaine 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-53-3, Chlorpromazine, analysis 50-55-5, Reserpine 50-60-2, Phentolamine 51-06-9, Procainamide 51-12-7, Nialamide 51-34-3, Scopolamine 51-41-2, Noradrenaline 51-45-6, Histamine, analysis 51-55-8, Atropine, analysis 51-67-2, Tyramine 51-71-8 52-53-9, Verapamil 52-86-8, Haloperidol 54-04-6, Mescaline 54-11-5, Nicotine 54-36-4, Metyrapone 54-49-9, Metaraminol 54-92-2, Iproniazid 55-73-2, Bethanidine 56-54-2, Quinidine 57-13-6, Urea, analysis 57-24-9, Strychnine 57-27-2, Morphine, analysis 57-42-1, Meperidine 57-47-6, Eserine 58-00-4, Apomorphine 58-08-2, Caffeine, analysis 58-25-3, Chlordiazepoxide 58-32-2, Dipyridamole 58-37-7, Aminopromazine 58-39-9, Perphenazine 58-40-2, Promazine 58-55-9,

Theophylline, analysis 58-73-1, Diphenhydramine 58-74-2, Papaverine 59-30-3, Folic Acid, analysis 59-42-7, Phenylephrine 59-46-1, Procaine 59-67-6, Nicotinic Acid, analysis 59-96-1, Phenoxybenzamine 59-98-3, Tolazoline 60-40-2, Mecamylamine 60-79-7, Ergonovine 60-87-7 60-91-3, Diethazine 60-99-1, Methotrimeprazine 61-00-7, Acepromazine 61-50-7 61-54-1, Tryptamine 61-78-9 62-67-9, Nalorphine 63-12-7, Benzquinamide 63-75-2, Arecoline 63-84-3 64-04-0, .beta.-Phenethylamine 64-95-9, Adiphenine 65-23-6, Pyridoxine 65-71-4, Thymine 66-22-8, Uracil, analysis 68-88-2, Hydroxyzine 69-23-8, Fluphenazine 71-63-6, Digitoxin 71-68-1, Dilaudid 72-44-6, Methaqualone 72-69-5, Nortriptyline 73-24-5, Adenine, analysis 74-89-5, Methylamine, analysis 75-50-3, Trimethylamine, analysis 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-99-3, Methadone 77-07-6, Levorphan 77-10-1, Phencyclidine 77-15-6, Ethoheptazine 77-19-0, Dicyclomine 77-20-3, Alphaprodine 77-22-5, Caramiphen 77-23-6, Carbetapentane 77-37-2, Procyclidine 77-38-3, Chlorphenoxamine 77-39-4, Cycrimine 78-51-3 81-13-0, Dexpanthenol 82-88-2 82-92-8, Cyclizine 83-67-0, Theobromine 83-74-9, Ibogaine 83-98-7, **Orphenadrine** 84-06-0, Thiopropazate 84-22-0, Tetrahydrozoline 85-18-7, 8-Chloro theophylline 85-79-0, Cinchocaine 86-13-5 86-21-5, Pheniramine 86-22-6, Brompheniramine 86-43-1, Propoxycaine 86-54-4, Hydralazine 87-00-3, Homatropine 90-39-1, Sparteine 90-69-7, Lobeline 90-82-4, Pseudoephedrine 90-84-6, Diethylpropion 91-80-5, Methapyrilene 91-81-6, Tripelennamine 91-82-7, Pyrrobutamine 91-84-9 91-85-0, Thonzylamine 92-12-6, Phenyltoloxamine 92-13-7, **Pilocarpine** 93-30-1, Methoxyphenamine 93-60-7, Methyl nicotinate 94-24-6, Tetracaine 94-25-7 94-78-0, Phenazopyridine 97-05-2, Sulfosalicylic acid 97-77-8, Disulfiram 98-92-0, Nicotinamide 99-43-4, Benoxinate 99-45-6, Adrenalone 100-55-0, Nicotinyl Alcohol 100-88-9, Cyclamic Acid 100-91-4, Eucatropine 101-40-6, Propylhexadrine 101-93-9, Phenacaine 102-45-4, Cyclopentamine 103-79-7, Phenyl acetone 103-82-2, Phenylacetic acid, analysis 104-31-4, Benzonatate 105-20-4, Betazole 107-43-7, Betaine 110-15-6, Butanedioic acid, analysis 110-60-1, Putrescine 110-89-4, Piperidine, analysis 113-15-5, Ergotamine 113-45-1, Methylphenidate 113-53-1, Dothiepin 113-59-7, Chlorprothixene 114-86-3, Phenformin 115-46-8, Azacyclonol 117-89-5, Trifluoperazine 117-96-4, Diatrizoate 118-23-0, Bromodiphenhydramine 120-57-0, Piperonal 125-29-1, Hydrocodone 125-30-4, Dionin 125-53-1, Oxyphencyclimine 125-71-3, Dextromethorphan 125-73-5, Dextrorphan 128-37-0, Butylated hydroxytoluene, analysis 129-03-3, Cyproheptadine 130-86-9, Protopine 131-28-2, Narceine 132-22-9 133-16-4, Chloro procaine 134-49-6, Phenmetrazine 137-58-6, Lidocaine 138-56-7, Trimethobenzamide 140-65-8, Pramoxine 143-57-7, Protoveratrine 144-11-6, Trihexyphenidyl 144-14-9, Anileridine 144-62-7, Ethanedioic acid, analysis 146-22-5, Nitrazepam 146-36-1, Azapetine 146-48-5, Yohimbine 146-54-3, Fluopromazine 147-20-6, Diphenylpyraline 149-16-6, Butacaine 150-59-4, Alverine 152-02-3, Levallorphan 153-76-4, Gallamine 155-09-9, Tranylcypromine 156-38-7 156-43-4, p-Phenetidine 244-63-3, Norharman 256-96-2, Iminostilbene 299-42-3, Ephedrine 300-62-9, Amphetamine 302-27-2, Aconitine 302-33-0, Proadifen 303-48-0, Desmethylclomipramine 303-49-1, Clomipramine 303-53-7, Cyclobenzaprine 304-21-2, Harmaline 309-29-5, Doxapram 315-30-0, Allopurinol 316-81-4, Thioproperazine 317-34-0, Aminophylline 340-57-8, Mecloqualone 357-57-3, Brucine 359-83-1, Pentazocine 361-37-5, Methysergide 364-62-5 364-98-7, Diazoxide 365-26-4, Hydroxyephedrine 390-28-3, Methoxamine 390-64-7, Prenylamine 395-28-8 396-01-0, Triamterene 404-86-4, Capsaicin 435-97-2,

Phenprocoumon 437-38-7, Fentanyl 437-74-1 438-60-8, Protriptyline 439-14-5, Diazepam 442-51-3, Harmine 447-41-6, Buphenine 458-24-2, Fenfluramine 458-88-8, Coniine 462-94-2, Cadaverine 465-65-6, Naloxone 467-85-6, Normethadone 469-21-6 469-62-5, Propoxyphene 476-69-7, Corydine 479-18-5, Diprophylline 486-12-4, Triprolidine 486-56-6, Cotinine 486-84-0, Harman 499-67-2, Proparacaine 503-01-5, Isometheptene 511-08-0, Ergocristine 511-09-1, Ergocryptine 511-12-6, Dihydroergotamine 512-15-2, Cyclopentolate 517-66-8, Dicentrine 519-09-5, Benzoylecgonine 519-37-9, Oxyethyltheophylline 520-52-5, Psilocybin 520-53-6, Psilocin 522-00-9, Ethopropazine 522-66-7, Hydroquinine 523-87-5, Dimenhydrinate 525-66-6, Propranolol
RL: ANT (Analyte); ANST (Analytical study)
(capillary zone electrophoresis in a comprehensive screen for basic drugs in whole blood)

L26 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2002 ACS

AB Principal components anal. (PCA) of standardized RF values of 443 drugs and their metabolites present in urine and blood samples chromatographed with four sheet systems provided a two-component model accounting for 70.8% of the total variance. The "scores" plot enabled either identification, or restriction of the range of inquiry to few candidates. This simple, cheap and fast anal. method is of vital importance in the identification of an unknown drug in cases of overdose intoxication or poisoning.

ACCESSION NUMBER: 1994:644897 CAPLUS
DOCUMENT NUMBER: 121:244897
TITLE: Qualitative organic analysis. Part 3. Identification of drugs and their metabolites by PCA of standardized TLC data
AUTHOR(S): Romano, Guido; Caruso, Giuseppe; Musumarra, Giuseppe; Pavone, Didier; Cruciani, Gabriele
CORPORATE SOURCE: Istituto di Medicina Legale e delle Assicurazioni, Univ. Catania, Catania, 95124, Italy
SOURCE: J. Planar Chromatogr.--Mod. TLC (1994), 7(3), 233-41
CODEN: JPCTE5; ISSN: 0933-4173
DOCUMENT TYPE: Journal
LANGUAGE: English
SO J. Planar Chromatogr.--Mod. TLC (1994), 7(3), 233-41
CODEN: JPCTE5; ISSN: 0933-4173
IT 50-36-2, Cocaine 50-37-3, Lysergide 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-52-2, Thioridazine 50-53-3, analysis 50-55-5, Reserpine 50-60-2, Phentolamine 51-06-9, Procainamide 51-34-3, Scopolamine 51-55-8, Atropine, analysis 51-68-3, Meclofenoxate 52-53-9, Verapamil 52-53-9D, Verapamil, metabolites 52-86-8, Haloperidol 54-03-5, Hexobendine 54-05-7, Chloroquine 54-11-5, Nicotine 54-31-9, Furosemide 54-32-0, Moxisylyte 54-85-3, Isoniazid 55-65-2, Guanethidine 56-54-2, Quinidine 57-24-9, Strychnine 57-27-2, Morphine, analysis 57-42-1, Meperidine 57-96-5, Sulfinpyrazone 58-08-2, Caffeine, analysis 58-15-1, Aminopyrine 58-25-3, Chlordiazepoxide 58-32-2, Dipyridamole 58-38-8, Prochlorperazine 58-39-9, Perphenazine 58-40-2, Promazine 58-55-9, Theophylline, analysis 58-73-1, Diphenhydramine 58-74-2, Papaverine 59-26-7, Niketamide 59-46-1, Procaine 59-87-0, Nitrofurazone 60-80-0, Antipyrine 60-87-7, Promethazine 60-99-1, Methotrimeprazine 61-00-7, Acepromazine 62-44-2, Phenacetin 62-67-9, Nalorphine 64-86-8 64-95-9, Adiphenine 68-88-2, Hydroxizine 68-89-3, Dipyrone 69-23-8, Fluphenazine 69-43-2, Prenylamine lactate

72-44-6, Methaqualone 72-69-5, Nortriptyline 73-09-6, Etozolin 74-55-5, Ethambutol 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-58-4, Ethylmorphine 76-99-3, Methadone 76-99-3D, Methadone, metabolites 77-07-6, Levorphanol 77-10-1, Phencyclidine 77-15-6, Ethoheptazine 77-19-0, Dicyclomine 77-37-2, Procyclidine 77-39-4, Cycrimine 77-67-8, Ethosuximide 80-77-3, Chlormezanone 82-88-2 82-92-8, Cyclizine 82-98-4, Piperidolate 83-07-8 83-15-8 83-67-0, Theobromine 83-98-7, **Orphenadrine** 84-22-0, Tetrahydrozoline 84-36-6, Syrosingopine 84-55-9, Viquidil 86-12-4 86-21-5, Pheniramine 86-22-6, Brompheniramine 86-42-0, Amodiaquin 86-75-9, Benzoxiquine 90-39-1, Sparteine 90-54-0, Etafenone 91-79-2, Thenyldiamine 91-81-6, Tripelenamine 91-84-9 92-12-6, Phenyltoloxamine 92-13-7, **Pilocarpine** 93-30-1, Methoxyphenamine 96-88-8, Mepivacaine 97-77-8, Disulfiram 99-43-4, Benoxinate 100-92-5, Mephentermine 101-40-6, Propylhexedrine 102-45-4, Cyclopentamine 113-42-8, Methylergonovine 113-45-1, Methylphenidate 113-53-1, Dothiepin 113-59-7, Chlorprothixene 113-92-8, Chlorpheniramine maleate 114-86-3, Phenformin 117-89-5, Trifluoperazine 120-29-6, Tropine 125-28-0, Dihydrocodeine 126-27-2, Oxethazaine 127-35-5, Phenazocine 128-62-1, Noscapine 130-26-7, Iodochlorhydroxyquin 130-95-0, Quinine 134-49-6, Phenmetrazine 137-58-6, Lidocaine 138-56-7, Trimethobenzamide 144-11-6, Trihexyphenidyl 146-22-5 146-48-5, Yohimbine 146-54-3, Triflupromazine 152-02-3, Levallorphan 156-08-1, Benzphetamine 298-46-4, Carbamazepine 298-57-7, Cinnarizine 299-42-3 300-62-9, Amphetamine 303-49-1, Clomipramine 303-49-1D, Clomipramine, metabolites 303-53-7, Cyclobenzaprine 309-29-5, Doxapram 314-35-2, Etamiphyllin 317-34-0, Aminophylline 318-23-0, Imolamine 357-57-3, Brucine 359-83-1, Pentazocine 361-37-5, Methysergide 364-62-5, Metoclopramide 372-66-7, Heptaminol 395-28-8, Isoxsuprine 437-38-7, Fentanyl 438-60-8, Protriptyline 439-14-5, Diazepam 443-48-1, Metronidazole 458-24-2, Fenfluramine 465-65-6, Naloxone 466-99-9, Hydromorphone 468-61-1, Oxeladin 469-21-6 469-62-5, Propoxyphene 479-92-5, Propyphenazone 482-15-5, Isothipendyl 483-04-5, Ajmalicine 493-92-5, Prolintane 501-68-8, Beclamide 510-53-2, Racemethorphan 511-12-6, Dihydroergotamine 511-45-5, Pridinol 512-15-2, Cyclopentolate 514-65-8, Biperiden 519-09-5, Benzoylecgonine 519-98-2 523-87-5, Dimenhydrinate 524-81-2, Mebhydrolin 525-66-6, Propranolol 526-36-3, Xylometazoline 537-26-8, Tropacocaine 537-46-2, Methamphetamine 539-15-1, Hordenine 548-73-2, Droperidol 553-06-0, N-(1,2-Diphenylethyl)nicotinamide 561-27-3, Diacetylmorphine 604-51-3, Deptropine 604-75-1 633-47-6, Cropropamide 634-03-7, Phendimetrazine 642-72-8, Benzydamine 738-70-5, Trimethoprim 739-71-9, Trimipramine 749-13-3, Trifluoperidol 768-94-5, Amantadine 791-35-5, Chlophedianol 804-10-4, Chromonar 835-31-4, Naphazoline 841-77-0, Norcyclizine 846-49-1, Lorazepam 846-50-4, Temazepam 848-75-9, Lormetazepam 852-42-6, Guaiapate 894-76-8, 7-Aminodesmethylflunitrazepam 911-45-5, Clomiphene 915-30-0, Diphenoxylate 952-54-5, Morphazinamide 959-14-8, Oxolamine 982-24-1, Clopenthixol 1028-33-7, Pentifylline 1088-11-5, Desmethyldiazepam 1092-46-2, Ketocaine 1098-97-1, Pyritinol 1165-48-6, Dimefline 1222-57-7, Zolimidine 1420-55-9, Thiethylperazine 1421-14-3, Propanidid 1435-55-8, Hydroquinidine 1491-59-4, Oxymetazoline 1617-90-9, Vincamine 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 1668-19-5, Doxepin 1672-58-8 1812-30-2, Bromazepam 1882-26-4, Pyridinolcarbamate 1893-33-0, Pipamperone 1951-25-3, Amiodarone 1977-10-2, Loxapine 2016-63-9, Bamifylline 2058-52-8, Clothiapine 2062-78-4, Pimozide 2167-85-3, Pipazethate 2180-92-9, Bupivacaine

2470-73-7, Dixyrazine 2558-30-7, Desmethylflunitrazepam 2609-46-3, Amiloride 2622-26-6, Pericyazine 2784-73-8, 6-Monoacetylmorphine 2886-65-9, N-1-Desalkylflurazepam 2894-67-9, Delorazepam 2898-12-6, Medazepam 2955-38-6, Prazepam 3099-52-3, Nicametate 3572-43-8, Bromhexine 3605-01-4, Piribedil 3625-06-7, Mebeverine 3703-76-2, Cloperastine 3703-79-5, Bamethan 3737-09-5, Disopyramide 3820-67-5, Glafenine 3930-20-9, Sotalol 4093-35-0, Bromopride
RL: ANT (Analyte); ANST (Analytical study)
(identification of drugs and metabolites in blood and urine by principal components anal. of standardized thin-layer chromatog. data)

L26 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2002 ACS

AB The combined use of normal and reversed-phase (RP) TLC in drug screening was evaluated by the mean list length method. A reversed-phase system, involving RP-18 plates and aq. HCl-MeOH as a mobile phase, was an effective complementary pair to basic medium-polar normal phase systems. With a set of 140 basic and quaternary drugs, a mean list of 1.8 was obtained for a TLC/RPTLC pair. The combination is also applicable to hydrophilic drugs extd. as bis(2-ethylhexyl) phosphate ion-pairs.

ACCESSION NUMBER: 1991:478997 CAPLUS
DOCUMENT NUMBER: 115:78997
TITLE: Combined use of normal and reversed-phase thin-layer chromatography in the screening for basic and quarternary drugs
AUTHOR(S): Ojanpera, Ilkka; Vartiovaara, Juhani; Ruohonen, Aira; Vuori, Erkki
CORPORATE SOURCE: Dep. Forensic Med., Univ. Helsinki, Helsinki, SF-00300, Finland
SOURCE: J. Liq. Chromatogr. (**1991**), 14(8), 1435-46
CODEN: JLCHD8; ISSN: 0148-3919
DOCUMENT TYPE: Journal
LANGUAGE: English
SO J. Liq. Chromatogr. (**1991**), 14(8), 1435-46
CODEN: JLCHD8; ISSN: 0148-3919

IT 50-36-2, Cocaine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-52-2, Thioridazine 50-53-3, Chlorpromazine, analysis 50-55-5, Reserpine 51-06-9, Procainamide 51-12-7, Nialamide 51-34-3, Scopolamine 51-55-8, Atropine, analysis 51-83-2, Carbachol 52-53-9, Verapamil 52-86-8, Haloperidol 54-04-6 54-05-7, Chloroquine 56-54-2, Quinidine 57-27-2, analysis 57-42-1, Pethidine 57-94-3, Tubocurarine 58-32-2 58-38-8, Prochlorperazine 58-39-9, Perphenazine 58-40-2, Promazine 58-73-1, Diphenhydramine 59-46-1, Procaine 59-99-4, Neostigmine 60-54-8, Tetracycline 60-87-7, Promethazine 60-99-1, Levomepromazine 62-67-9, Nalorphine 68-88-2, Hydroxyzine 69-23-8, Fluphenazine 72-69-5, Nortriptyline 76-42-6, Oxycodone 76-57-3, Codeine 76-58-4, Ethylmorphine 76-99-3, Methadone 82-92-8, Cyclizine 83-98-7, **Orphenadrine** 84-96-8, Trimeprazine 86-21-5, Pheniramine 86-54-4, Hydralazine 90-84-6, Amfepramone 91-84-9, Mepyramine 92-13-7, **Pilocarpine** 96-88-8, Mepivacaine 113-59-7, Chlorprothixene 117-89-5, Trifluoperazine 118-42-3, Hydroxychloroquine 122-09-8, Phentermine 125-71-3, Dextromethorphan 128-62-1, Noscapine 130-95-0, Quinine 137-58-6, Lidocaine 147-20-6, Diphenylpyraline 153-87-7, Oxypertine 298-57-7, Cinnarizine 299-42-3 300-62-9, Amphetamine 303-49-1, Clomipramine 306-40-1, Suxamethonium 315-72-0, Opipramol 316-81-4, Thioproperazine 359-83-1, Pentazocine 364-62-5, Metoclopramide 396-01-0, Triamterene 438-60-8, Protriptyline 458-24-2, Fenfluramine 469-62-5, Dextropropoxyphene 486-12-4, Triprolidine 493-92-5, Prolintane 514-65-8, Biperiden 525-66-6,

Propranolol 537-46-2, Methamphetamine 569-65-3, Meclozine 586-06-1, Orciprenaline 596-51-0 657-24-9, Metformin 721-50-6, Prilocaine 739-71-9, Trimipramine 768-94-5, Amantadine 1050-79-9, Moperone 1131-64-2, Debrisoquine 1209-98-9, Fencamfamin 1420-55-9, Thiethylperazine 1668-19-5, Doxepin 2062-78-4, Pimozide 2180-92-9, Bupivacaine 2470-73-7, Dixyrazine 2609-46-3, Amiloride 2622-26-6, Periciazine 2709-56-0, Flupenthixol 2751-68-0, Acetophenazine 3575-80-2, Melperone 3737-09-5, Disopyramide 3930-20-9, Sotalol 4205-90-7, Clonidine 4360-12-7, Ajmaline 4498-32-2, Dibenzepin 5591-45-7, Thiothixene 5636-83-9, Dimethindene 5786-21-0, Clozapine 6452-71-7, Oxprenolol 6673-35-4, Practolol 7182-53-8, Butylscopolammonium 10262-69-8, Maprotiline 13392-18-2, Fenoterol 13523-86-9, Pindolol 13655-52-2, Alprenolol 14838-15-4, Phenylpropanolamine 15676-16-1, Sulpiride 15686-51-8, Clemastine 17692-34-1, Etodroxizine 18559-94-9, Salbutamol 19216-56-9, Prazosin 19794-93-5, Trazodone 21829-25-4, Nifedipine 23031-25-6, Terbutaline 23214-96-2, Alcuronium 24219-97-4, Mianserin 25523-97-1, Dexchlorpheniramine 26839-75-8, Timolol 26864-56-2, Penfluridol 27892-33-7, Emepronium 29122-68-7, Atenolol 31828-71-4, Mexiletine 36894-69-6, Labetalol 37350-58-6, Metoprolol 37517-30-9, Acebutolol 38304-91-5, Minoxidil 41708-72-9, Tocainide 42399-41-7, Diltiazem 43200-80-2, Zopiclone 51481-61-9, Cimetidine 52485-79-7, Buprenorphine 53772-83-1, Zuclopenthixol 54063-52-4, Pitofenone 54063-53-5, Propafenone 54143-55-4, Flecainide 66357-35-5, Ranitidine 68844-77-9, Astemizole
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, by combined normal and reversed-phase TLC)

L26 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2002 ACS

AB A reliable and simple method for the routine anal. of pharmaceutical dosage forms by high-performance liq. chromatog. using a C18 Bondapak reversed-phase column with a binary solvent system consisting of MeCN and 0.05M KH2PO4 was developed. Standardized extn. procedures for drugs in various dosage forms were developed and successfully applied to a wide range of current pharmaceutical formulations.

ACCESSION NUMBER: 1987:182729 CAPLUS
DOCUMENT NUMBER: 106:182729
TITLE: General method for the analysis of pharmaceutical dosage forms by high-performance liquid chromatography
AUTHOR(S): Sidhu, A. S.; Kennedy, J. M.; Deeble, S.
CORPORATE SOURCE: Natl. Biol. Stand. Lab., Canberra, Australia
SOURCE: J. Chromatogr. (1987), 391(1), 233-42
CODEN: JOCRAM; ISSN: 0021-9673
DOCUMENT TYPE: Journal
LANGUAGE: English
SO J. Chromatogr. (1987), 391(1), 233-42
CODEN: JOCRAM; ISSN: 0021-9673
IT 50-33-9, Phenylbutazone, analysis 50-34-0, Propantheline bromide 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-52-2, Thioridazine 50-53-3, Chlorpromazine, analysis 51-48-9, analysis 51-55-8, Atropine, analysis 52-01-7, Spironolactone 52-53-9, Verapamil 52-86-8, Haloperidol 52-88-0, Atropine methonitrate 53-86-1, Indomethacin 54-05-7, Chloroquine 54-31-9, Frusemide 56-54-2, Quinidine 57-41-0, Phenytoin 57-42-1, Pethidine 57-66-9, Probenecid 57-68-1, Sulfadimidine 57-96-5, Sulfinpyrazone 58-25-3, Chlordiazepoxide 58-32-2, Dipyridamole 58-38-8, Prochlorperazine 58-54-8, Ethacrynic acid 58-73-1, Diphenhydramine 58-93-5, Hydrochlorothiazide 58-94-6, Chlorothiazide 59-63-2, Isocarboxazid

60-87-7, Promethazine 64-86-8, Colchicine 69-23-8, Fluphenazine
72-69-5, Nortriptyline 73-48-3, Bendrofluazide 73-49-4, Quinethazone
76-57-3, Codeine 77-36-1, Chlorthalidone 77-37-2, Procyclidine
83-98-7, **Orphenadrine** 86-22-6 86-34-0, Phensuximide
86-42-0, Amodiaquine 87-00-3, Homatropine 90-34-6, Primaquine
91-75-8, Antazoline 92-13-7, **Pilocarpine** 94-24-6,
Amethocaine 96-88-8 113-92-8, Chlorpheniramine maleate 114-80-7,
Neostigmine bromide 115-79-7, Ambenonium chloride 117-89-5,
Trifluoperazine 118-42-3, Hydroxychloroquine 127-69-5, Sulfafurazole
129-03-3, Cyproheptadine 130-95-0, Quinine 132-17-2, Benztropine
mesylate 132-20-7, Pheniramine maleate 135-07-9 137-58-6 144-11-6,
Benzhexol 144-80-9, Sulfacetamide 144-82-1, Sulfamethizole 146-22-5,
Nitrazepam 147-20-6, Diphenylpyraline 148-79-8, Thiabendazole
298-46-4, Carbamazepine 315-72-0, Opipramol 364-62-5 396-01-0,
Triamterene 438-60-8, Protriptyline 439-14-5, Diazepam 442-52-4,
Clemizole 443-48-1, Metronidazole 465-65-6, Naloxone 486-12-4,
Triprolidine 500-92-5, Proguanil 514-65-8, Biperiden 521-78-8,
Trimipramine maleate 525-66-6, Propranolol 599-79-1, Sulfasalazine
603-50-9, Bisacodyl 604-75-1, Oxazepam 721-50-6, Prilocaine
723-46-6, Sulfamethoxazole 738-70-5, Trimethoprim 742-20-1,
Cyclopenthiazide 835-31-4, Naphazoline 846-49-1, Lorazepam 846-50-4,
Temazepam 968-81-0, Acetohexamide 1131-64-2, Debrisoquine 1134-47-0,
Baclofen 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 1812-30-2,
Bromazepam 2127-01-7, Clorexolone 2180-92-9, Bupivacaine 2277-92-1
2609-46-3, Amiloride 2898-12-6, Medazepam 2922-44-3, Dextromoramide
tartrate 3485-62-9, Clidinium bromide 3614-69-5, Dimethindene maleate
3902-71-4 3978-86-7, Azatadine maleate 4205-90-7, Clonidine
5543-58-8 6153-33-9 6452-71-7 6893-02-3 7195-27-9, Mefruside
13392-18-2, Fenoterol 13523-86-9, Pindolol 13655-52-2, Alprenolol
14769-73-4 15180-03-7, Alcuronium chloride 15687-27-1, Ibuprofen
17560-51-9, Metolazone 17617-23-1, Flurazepam 19216-56-9, Prazosin
21187-98-4, Gliclazide 21829-25-4, Nifedipine 22204-53-1, Naproxen
22232-54-8, Carbimazole 22260-51-1, Bromocriptine mesylate 23256-50-0,
Guanabenz acetate 23593-75-1, Clotrimazole 24219-97-4 24359-22-6,
Pizotifen maleate 26921-17-5, Timolol maleate 27220-47-9, Econazole
28782-42-5, Difenoxin 32795-47-4, Nomifensine maleate 36894-69-6
38194-50-2, Sulindac 38304-91-5, Minoxidil 42399-41-7, Diltiazem
52365-63-6 53179-11-6 56392-17-7, Metoprolol tartrate 76095-16-4,
Enalapril maleate
RL: ANT (Analyte); ANST (Analytical study)
(HPLC of)

L26 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2002 ACS
AB The principal components (PC) anal. of standardized Rf values in 4 eluent systems [ethyl acetate-methanol-30% ammonia (85:10:15), cyclohexane-toluene-diethylamine (65:25:10), Et acetate-chloroform (50:50), and acetone with the plate dipped in KOH soln.] and of gas chromatog. retention indexes in SE 30 for 277 compds. provided a 2-PC model that explains 82% of the total variance. The scores plot allowed identification of unknowns or restriction of the range of inquiry to very few candidates. Comparison of these candidates with those selected from another PC model derived from thin-layer chromatog. data only allowed identification of the drug in all the examd. cases.
ACCESSION NUMBER: 1987:526383 CAPLUS
DOCUMENT NUMBER: 107:126383
TITLE: Qualitative organic analysis. Part 2. Identification of drugs by principal components analysis of standardized TLC data in four eluent systems and of

retention indexes on SE 30

AUTHOR(S): Musumarra, Giuseppe; Scarlata, Giuseppe; Romano, Guido; Cappello, Giuseppe; Clementi, Sergio; Giulietti, Gianfranco

CORPORATE SOURCE: Dip. Sci. Chim., Univ. Catania, Catania, 95125, Italy

SOURCE: J. Anal. Toxicol. (1987), 11(4), 154-63
CODEN: JATOD3; ISSN: 0146-4760

DOCUMENT TYPE: Journal

LANGUAGE: English

SO J. Anal. Toxicol. (1987), 11(4), 154-63
CODEN: JATOD3; ISSN: 0146-4760

IT 50-36-2, Cocaine 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 50-52-2, Thioridazine 50-53-3, Chlorpromazine, biological studies 50-58-8, Phendimetrazine bitartrate 51-34-3, Scopolamine 51-55-8, Atropine, biological studies 51-68-3, Meclofenoxate 52-53-9, Verapamil 52-86-8, Haloperidol 54-05-7, Chloroquine 54-11-5, Nicotine 54-32-0, Moxisylyte 54-85-3 56-54-2, Quinidine 57-24-9, Strychnine 57-27-2, Morphine, biological studies 57-42-1, Meperidine 58-08-2, Caffeine, biological studies 58-15-1, Aminopyrine 58-25-3 58-40-2, Promazine 58-73-1, Diphenhydramine 58-74-2, Papaverine 59-26-7, Nikethamide 59-46-1 60-80-0 60-87-7, Promethazine 60-99-1, Methotrimeprazine 62-44-2, Phenacetin 62-67-9, Nalorphine 68-88-2, Hydroxyzine 68-89-3, Dipyrone 69-23-8, Fluphenazine 69-43-2, Prenylamine lactate 71-82-9, Levallorphan tartrate 72-44-6 72-69-5, Nortriptyline 76-41-5, Oxymorphone 76-42-6, Oxycodone 76-57-3, Codeine 76-58-4, Ethylmorphine 76-99-3, Methadone 76-99-3D, metabolite 77-07-6, Levorphanol 77-15-6, Ethoheptazine 77-19-0, Dicyclomine 77-37-2 77-39-4, Cycrimine 77-67-8, Ethosuximide 80-77-3, Chlormezanone 82-92-8, Cyclizine 82-98-4, Piperidolate 83-98-7, **Orphenadrine** 84-02-6, Prochlorperazine dimaleate 84-55-9, Viquidil 86-22-6, Brompheniramine 86-75-9, Benzoxiquine 90-39-1, Sparteine 90-54-0, Etafenone 91-79-2, Thenyldiamine 92-12-6, Phenyltoloxamine 92-13-7, **Pilocarpine** 93-30-1, Methoxyphenamine 96-88-8, Mepivacaine 97-77-8, Disulfiram 99-43-4, Benoxinate 100-92-5, Mephentermine 101-40-6, Propylhexedrine 102-45-4, Cyclopentamine 113-45-1, Methylphenidate 113-59-7, Chlorprothixene 113-92-8, Chlorpheniramine maleate 117-89-5, Trifluoperazine 125-28-0, Dihydrocodeine 127-35-5, Phenazocine 128-62-1, Noscapine 129-03-3, Cyproheptadine 130-95-0 132-20-7, Pheniramine maleate 132-35-4, Proxazole citrate 134-49-6, Phenmetrazine 137-58-6, Lidocaine 144-11-6, Trihexyphenidyl 146-22-5, Nitrazepam 146-48-5, Yohimbine 146-54-3, Triflupromazine 156-08-1 298-46-4, Carbamazepine 298-57-7, Cinnarizine 299-42-3 300-62-9, Amphetamine 303-49-1, Clomipramine 309-29-5, Doxapram 314-35-2, Etamiphyllin 318-23-0, Imolamine 357-57-3, Brucine 359-83-1, Pentazocine 364-62-5, Metoclopramide 372-66-7, Heptaminol 395-28-8, Isoxsuprine 438-60-8 439-14-5, Diazepam 443-48-1, Metronidazole 458-24-2, Fenfluramine 465-65-6, Naloxone 469-62-5, Propoxyphene 479-92-5, Propyphenazone 482-15-5, Isothipendyl 493-92-5, Prolintane 501-68-8, Beclamide 510-53-2, Racemethorphan 511-12-6, Dihydroergotamine 512-15-2, Cyclopentolate 514-65-8, Biperiden 521-78-8, Trimipramine maleate 523-87-5, Dimenhydrinate 524-81-2 525-66-6, Propranolol 526-36-3, Xylometazoline 537-46-2, Methamphetamine 539-15-1, Hordenine 548-73-2, Droperidol 553-06-0 561-27-3, Diacetylmorphine 604-75-1 633-47-6, Cropropamide 634-03-7, Phendimetrazine 642-72-8, Benzydamine 738-70-5, Trimethoprim 749-13-3, Trifluperidol 768-94-5, Amantadine 791-35-5 804-10-4, Chromonar 841-77-0, Norcyclizine 846-49-1 846-50-4, Temazepam

848-75-9, Lormetazepam 852-42-6, Guaiapate 894-76-8, 7-Amino-desmethylflunitrazepam 990-73-8, Fentanyl citrate 1028-33-7, Pentifylline 1088-11-5 1092-46-2, Ketocaine 1165-48-6 1222-57-7, Zolimidine 1420-55-9, Thiethylperazine 1421-14-3, Propanidid 1435-55-8, Hydroquinidine 1617-90-9, Vincamine 1622-61-3, Clonazepam 1622-62-4, Flunitrazepam 1668-19-5, Doxepin 1812-30-2, Bromazepam 1893-33-0, Pipamperone 1949-20-8, Oxolamine citrate 2058-52-8, Clothiapine 2167-85-3, Pipazethate 2169-75-7 2180-92-9, Bupivacaine 2558-30-7, Desmethylflunitrazepam 2622-26-6, Pericyazine 2784-55-6 2784-73-8 2886-65-9 2894-67-9, Delorazepam 2898-12-6, Medazepam 2955-38-6, Prazepam 3099-52-3, Nicametate 3572-43-8, Bromhexine 3703-76-2, Cloperastine 3703-79-5, Bamethan 3737-09-5, Disopyramide 3820-67-5, Glafenine 3930-20-9, Sotalol 4093-35-0, Bromopride 4171-13-5, Valnoctamide 4205-90-7, Clonidine 4498-32-2, Dibenzepin 4551-59-1, Fenalamide 4630-95-9, Prifinium bromide 4969-02-2, Methixene 5036-02-2, Tetramisole 5053-06-5, Fenspiride 5118-29-6, Melitracen 5636-83-9, Dimethindene 5741-22-0, Moprolol 6168-76-9, Crotethamide 6452-71-7, Oxprenolol 6493-05-6, Pentoxifylline 6506-37-2, Nimorazole 6724-53-4, Perhexiline maleate 6740-88-1, Ketamine 6856-31-1 7262-75-1, Lefetamine 7456-24-8, Fonazine 10262-69-8, Maprotiline 10418-03-8, Stanozolol 10539-19-2, Moxaverine 11032-41-0, Dihydroergotoxine 13042-18-7, Fendiline 13523-86-9, Pindolol 13669-70-0, Nefopam 14007-64-8, Butethamate 14698-07-8, Tipepidine citrate 14860-49-2, Clobutinol 15301-69-6, Flavoxate 15686-51-8, Clemastine 15687-41-9, Oxyfedrine 17449-96-6, Clofezone 17617-23-1, Flurazepam 17692-51-2, Metergoline 17854-59-0, Mepixanthone 18046-21-4, Fentiazac 18053-31-1, Fominoben 18109-81-4, Butamirate citrate 18683-91-5, Ambroxol 19794-93-5, Trazodone 20448-86-6, Bornaprine 20971-53-3 21363-18-8, Viminol 21829-25-4, Nifedipine 21888-98-2, Dexetimide 22131-35-7, Butalamine 22232-71-9, Mazindol 22316-47-8, Clobazam 22916-47-8, Miconazole 23602-78-0, Benfluorex 23779-99-9, Floctafenine 23887-31-2, Clorazepate 24219-97-4, Mianserin 24359-22-6 24526-64-5, Nomifensine 25146-18-3, Febutol 26839-75-8, Timolol 28911-01-5 29769-70-8 29975-16-4, Estazolam
RL: PROC (Process)
(identification of, by principle components anal. of Thin layer chromtog. data and gas chromatog. retention)

L26 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2002 ACS
AB Spiro-(N'-methylpiperidyl-4')-N-ethyl succinimide hydrogen fumarate, eserine, and **pilocarpine** nitrate rapidly abolished the abnormal involuntary movements induced in guinea pigs by intrastriatal dopamine [51-61-6] (100 .mu.g). Dexbenzetimide, atropine sulfate, and **orphenadrine**-HCl did not potentiate the effect of dopamine (25 .mu.g), but pretreatment with these agents prevented the effects of the cholinomimetics. This suggested that an acetylcholine system moderates a dopamine dysfunction in dyskinesias.

ACCESSION NUMBER: 1975:508820 CAPLUS
DOCUMENT NUMBER: 83:108820
TITLE: Cholinergic modification of abnormal involuntary movements induced in the guinea pig by intrastriatal dopamine
AUTHOR(S): Costall, B.; Naylor, R. J.
CORPORATE SOURCE: Postgrad. Sch. Stud. Pharmacol., Univ. Bradford, Bradford, Engl.
SOURCE: J. Pharm. Pharmacol. **(1975)**, 27(4), 273-5
CODEN: JPPMAB

DOCUMENT TYPE: Journal
LANGUAGE: English
SO J. Pharm. Pharmacol. (**1975**), 27(4), 273-5
CODEN: JPPMAB
AB Spiro-(N'-methylpiperidyl-4')-N-ethyl succinimide hydrogen fumarate, eserine, and **pilocarpine** nitrate rapidly abolished the abnormal involuntary movements induced in guinea pigs by intrastriatal dopamine [51-61-6] (100 .mu.g). Dexbenzetimide, atropine sulfate, and **orphenadrine**-HCl did not potentiate the effect of dopamine (25 .mu.g), but pretreatment with these agents prevented the effects of the cholinomimetics. This suggested that an acetylcholine system moderates a dopamine dysfunction in dyskinesias.

L26 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2002 ACS
AB The peripheral and central anticholinergic properties of benzetimide (R 4929) and a series of 22 other atropine-like drugs, such as atropine sulfate, homatropine-HCl, scopolamine-HCl, isopropamide iodide, hexamethamide, diphenhydramine-HCl, **orphenadrine**-HCl, trihexyphenidyl-HCl, and methixene-HCl were measured in a new antipilocarpine test in rats. The method, in which a variety of central and peripheral anticholinergic effects, such as mydriasis, piloerection, chewing, tremor, lacrimation, and salivation, could be measured simultaneously in the same animal was described. The results indicated that benzetimide at various geometrically spaced dose levels (0.0025-160 mg./kg.) and the chem. related compds., meletimide (R 5183) and cinperene (R 5046) were the only drugs that could block **pilocarpine** -induced lacrimation or salivation at submydriatic dose levels. Furthermore, the relative central anticholinergic potency of these 3 drugs were quite high and comparable with that of benzatropine and other anticholinergics that were clin. used as antiparkinson agents. 41 references.
ACCESSION NUMBER: 1967:480994 CAPLUS
DOCUMENT NUMBER: 67:80994
TITLE: Peripheral and central anticholinergic properties of benzetimide (R 4929) and other atropine-like drugs as measured in a new antipilocarpine test in rats
AUTHOR(S): Janssen, Paul A. J.; Niemegeers, Carlos J. E.
CORPORATE SOURCE: Janssen Pharm. Res. Lab., Beerse, Belg.
SOURCE: Psychopharmacologia (**1967**), 11(3), 231-54
CODEN: PSYPAG
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Psychopharmacologia (**1967**), 11(3), 231-54
CODEN: PSYPAG
AB The peripheral and central anticholinergic properties of benzetimide (R 4929) and a series of 22 other atropine-like drugs, such as atropine sulfate, homatropine-HCl, scopolamine-HCl, isopropamide iodide, hexamethamide, diphenhydramine-HCl, **orphenadrine**-HCl, trihexyphenidyl-HCl, and methixene-HCl were measured in a new antipilocarpine test in rats. The method, in which a variety of central and peripheral anticholinergic effects, such as mydriasis, piloerection, chewing, tremor, lacrimation, and salivation, could be measured simultaneously in the same animal was described. The results indicated that benzetimide at various geometrically spaced dose levels (0.0025-160 mg./kg.) and the chem. related compds., meletimide (R 5183) and cinperene (R 5046) were the only drugs that could block **pilocarpine** -induced lacrimation or salivation at submydriatic dose levels. Furthermore, the relative central anticholinergic potency of these 3 drugs

were quite high and comparable with that of benzatropine and other anticholinergics that were clin. used as antiparkinson agents. 41 references.

L26 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2002 ACS

AB cf. CA 51, 1538i. A new method was perfected for identifying 161 medicinals, both natural compds. (e.g., **pilocarpine**) and synthetic (e.g., tetracaine), which involves sepn. of the substances into 3 groups by extn. first at a low pH, then at a high pH, and then using an ion exchanger. The further sepn. of each group is then done with paper chromatography (PC) with thin-layer chromatography (TLC) also serving for identification of the individual compds. A diversity of mobile solvent systems (13 for PC and 13 for TLC) and reagents (17 for PC and 2 for TLC, also uv light) is given for the various compds. The Rf values, spot colors, and special features are all tabulated for these compds. The aq. soln. is acidified with HCl to pH 3-4 and repeatedly shaken out with Et2O; the aq. ext. is then shaken with NaHCO3 to pH 10-11 and extd. several times with Et2O. The exts. are dried over Na2SO4 and evapd., the small residue being dissolved in alc. To the original aq. soln. a cation exchanger is added, stirred, filtered out, washed with N HCl, the acid exts. are combined and evapd. on a water bath, and the salts of the quaternary bases dissolved in warm alc. By following this procedure, only 5 compds. could not be fully sepd., viz., the pairs of barbital and pentobarbital, methylergometrine and apomorphine, **orphenadrine** -alfadryl, and antiparkin-methadone. However, these could be detected by reagent tests or after elution spectrophotometry. 14 references.

ACCESSION NUMBER: 1966:3297 CAPLUS
DOCUMENT NUMBER: 64:3297
ORIGINAL REFERENCE NO.: 64:527b-d
TITLE: New procedures for systematic analysis of medicinals by paper and thin-layer chromatography
AUTHOR(S): Macek, K.; Vecerkova, J.
CORPORATE SOURCE: Forschungsinst. Pharm. Biochem., Prague
SOURCE: Pharmazie (**1965**), 20(10), 605-16
DOCUMENT TYPE: Journal
LANGUAGE: German

SO Pharmazie (**1965**), 20(10), 605-16

AB cf. CA 51, 1538i. A new method was perfected for identifying 161 medicinals, both natural compds. (e.g., **pilocarpine**) and synthetic (e.g., tetracaine), which involves sepn. of the substances into 3 groups by extn. first at a low pH, then at a high pH, and then using an ion exchanger. The further sepn. of each group is then done with paper chromatography (PC) with thin-layer chromatography (TLC) also serving for identification of the individual compds. A diversity of mobile solvent systems (13 for PC and 13 for TLC) and reagents (17 for PC and 2 for TLC, also uv light) is given for the various compds. The Rf values, spot colors, and special features are all tabulated for these compds. The aq. soln. is acidified with HCl to pH 3-4 and repeatedly shaken out with Et2O; the aq. ext. is then shaken with NaHCO3 to pH 10-11 and extd. several times with Et2O. The exts. are dried over Na2SO4 and evapd., the small residue being dissolved in alc. To the original aq. soln. a cation exchanger is added, stirred, filtered out, washed with N HCl, the acid exts. are combined and evapd. on a water bath, and the salts of the quaternary bases dissolved in warm alc. By following this procedure, only 5 compds. could not be fully sepd., viz., the pairs of barbital and pentobarbital, methylergometrine and apomorphine, **orphenadrine** -alfadryl, and antiparkin-methadone. However, these could be detected by reagent tests or after elution spectrophotometry. 14 references.

09/214,851

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=> d his

     (FILE 'HOME' ENTERED AT 17:15:02 ON 10 APR 2002)

     FILE 'REGISTRY' ENTERED AT 17:15:12 ON 10 APR 2002
                E METHOXSALEN/CN
L1              1 S E3

     FILE 'CAPLUS, USPATFULL' ENTERED AT 17:15:41 ON 10 APR 2002
L2           2642 S L1
L3           2782 S (L2 OR METHOXSALEN?)
L4             52 S L3 AND (NICOTINE OR CYP2A6 OR COTININE OR TOBACCO OR SMOKING)
L5             52 DUP REM L4 (0 DUPLICATES REMOVED)
L6             17 S L5 AND PY<=1996
L7              4 S L4 AND CYP2B6
L8              0 S L5 AND PY<=199
L9             28 S L5 AND PY<=1999
L10           489 S ORPHENADRIN?
L11            80 S L10 AND (NICOTINE OR CYP2A6 OR COTININE OR TOBACCO OR SMOKING
L12            80 DUP REM L11 (0 DUPLICATES REMOVED)
L13            57 S L12 AND PY<=1999
L14            22 S CYP2B6(P)(INHIBITOR OR ANTAGONSIT#) AND (NICOTINE OR CYP2A6 O
L15            19 S L14 AND PY <=1999
L16             0 S CYP2B6(P)(INHIBITOR OR ANTAGONIST#) AND (NICOTINE OR TOBACCO
L17            74 S L10 AND (NICOTINE OR COTININE OR TOBACCO OR SMOKING)
L18            51 S L17 AND PY<=1999
L19            42 S L17 AND PY<=1997

     FILE 'STNGUIDE' ENTERED AT 17:49:59 ON 10 APR 2002

     FILE 'CAPLUS, USPATFULL' ENTERED AT 17:54:34 ON 10 APR 2002
L20             2 S L3 AND ORPHENADRIN?
L21             2 DUP REM L20 (0 DUPLICATES REMOVED)
L22            19 S L4 AND PY<=1997
L23            52 S PILOCARPIN? AND ORPHENADRIN?
L24             1 S PILOCARPIN? AND CYP2B6(P)(INHIBITOR# OR ANTAGONIST#)
L25            16 S L23 AND PY<=1997
L26            16 DUP REM L25 (0 DUPLICATES REMOVED)

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=> s (miconazol? or clotrimazol? or aflatoxin(2a)B or coumarin? or furanocoumarin? or imperatorin? or isopimpinellin? or sphondin? or bergapten? or naringenin? or racumin? or nitropyren? or menadion?) and cyp2b6
L30 43 (MICONAZOL? OR CLOTRIMAZOL? OR AFLATOXIN(2A) B OR COUMARIN? OR FURANOCOUMARIN? OR IMPERATORIN? OR ISOPIMPINELLIN? OR SPHONDIN? OR BERGAPTEN? OR NARINGENIN? OR RACUMIN? OR NITROPYREN? OR MENAD ION?) AND CYP2B6

=> s l30 and py<=1997
L31 14 L30 AND PY<=1997

=> d l31 abs ibib kwic 1-14

L31 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2002 ACS
AB Comparison of 7-hydroxylation of **coumarin**, a CYP2A6 substrate, in human and African green and cynomolgus monkey liver microsomes was made by an HPLC assay with UV detection. In human liver microsomes, the Km and Vmax values for the metabolic conversion were 2.1 .mu.M and 0.79 nmol/mg/min, resp. While African green monkey showed Km and Vmax values of 2.7 .mu.M and 0.52 nmol/mg/min, which were similar to human, higher Km and Vmax values were found in cynomolgus monkey. **Coumarin** 7-hydroxylation in human and African green monkey was selectively inhibited by methoxsalen and pilocarpine (CYP2A6 inhibitors) but not by other inhibitors, i.e. .alpha.-naphthoflavone (CYP1A1), orphenadrine (**CYP2B6**), sulfaphenazole (CYP2C9), quinidine (CYP2D6), and ketoconazole (CYP3A4). Immunoinhibition results supported CYP2A6 involvement in human and its homolog in monkey in **coumarin** 7-hydroxylation, as only anti-CYP2A6, but not CYP2B1, CYP2C13, CYP2D6, CYP2E1, or CYP3A antibodies, inhibited this conversion. African green monkey was similar to human in catalytic activity of **coumarin** 7-hydroxylation and response to CYP2A6 inhibitors or antibody inhibition. However, the monkey CYP2A6 is not identical to the human in that Ki values were different, and differences were obsd. with some CYP2A6 inhibitors, such as nicotine and methoxsalen, suggesting that, under some circumstances, studies of nicotine kinetics and drug taking behavior in monkey may not be comparable to human.
ACCESSION NUMBER: 1998:150136 CAPLUS
DOCUMENT NUMBER: 128:164257
TITLE: Comparison of CYP2A6 catalytic on **coumarin** 7-hydroxylation in human and monkey liver microsomes
AUTHOR(S): Li, Yan; Li, Ning Yuan; Sellers, Edward M.
CORPORATE SOURCE: Dep. Pharmacology, Medicine, Psychiatry, Univ. Toronto, Toronto, ON, M5S 1A8, Can.
SOURCE: Eur. J. Drug Metab. Pharmacokinet. (**1997**), 22(4), 295-304
CODEN: EJDPD2; ISSN: 0378-7966
PUBLISHER: Medecine et Hygiene
DOCUMENT TYPE: Journal
LANGUAGE: English
TI Comparison of CYP2A6 catalytic on **coumarin** 7-hydroxylation in human and monkey liver microsomes
SO Eur. J. Drug Metab. Pharmacokinet. (**1997**), 22(4), 295-304
CODEN: EJDPD2; ISSN: 0378-7966
AB Comparison of 7-hydroxylation of **coumarin**, a CYP2A6 substrate, in human and African green and cynomolgus monkey liver microsomes was made by an HPLC assay with UV detection. In human liver microsomes, the Km and Vmax values for the metabolic conversion were 2.1 .mu.M and 0.79

nmol/mg/min, resp. While African green monkey showed Km and Vmax values of 2.7 .mu.M and 0.52 nmol/mg/min, which were similar to human, higher Km and Vmax values were found in cynomolgus monkey. **Coumarin** 7-hydroxylation in human and African green monkey was selectively inhibited by methoxsalen and pilocarpine (CYP2A6 inhibitors) but not by other inhibitors, i.e. .alpha.-naphthoflavone (CYP1A1), orphenadrine (**CYP2B6**), sulfaphenazole (CYP2C9), quinidine (CYP2D6), and ketoconazole (CYP3A4). Immunoinhibition results supported CYP2A6 involvement in human and its homolog in monkey in **coumarin** 7-hydroxylation, as only anti-CYP2A6, but not CYP2B1, CYP2C13, CYP2D6, CYP2E1, or CYP3A antibodies, inhibited this conversion. African green monkey was similar to human in catalytic activity of **coumarin** 7-hydroxylation and response to CYP2A6 inhibitors or antibody inhibition. However, the monkey CYP2A6 is not identical to the human in that Ki values were different, and differences were obsd. with some CYP2A6 inhibitors, such as nicotine and methoxsalen, suggesting that, under some circumstances, studies of nicotine kinetics and drug taking behavior in monkey may not be comparable to human.

ST cytochrome P450 **coumarin** hydroxylation enzyme kinetics; Michaelis const cytochrome P450 **coumarin** hydroxylation; monkey microsome cytochrome P450 **coumarin** hydroxylation

IT Enzyme kinetics
Michaelis constant
Microsome
Monkey
(comparison of CYP2A6 catalytic on **coumarin** 7-hydroxylation in human and monkey liver microsomes)

IT Monoclonal antibodies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(selective inhibition of **coumarin** 7-hydroxylation by CYP2A6 monoclonal antibody)

IT 9035-51-2, Cytochrome P 450, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(CYP2A6; comparison of CYP2A6 catalytic on **coumarin** 7-hydroxylation in human and monkey liver microsomes)

IT 93-35-6, 7-Hydroxycoumarin
RL: BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(comparison of CYP2A6 catalytic on **coumarin** 7-hydroxylation in human and monkey liver microsomes)

IT 91-64-5, **Coumarin**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(comparison of CYP2A6 catalytic on **coumarin** 7-hydroxylation in human and monkey liver microsomes)

IT 147-84-2, Diethyldithiocarbamic acid, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(inhibition of **coumarin** 7-hydroxylation by)

IT 92-13-7, Pilocarpine 298-81-7, Methoxsalen
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(selective inhibition of **coumarin** 7-hydroxylation by)

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AB Sequential oxidns. at the arylamine moiety of the procainamide mol. leading to the formation of N-hydroxyprocainamide and its nitroso deriv.

may be responsible for lupus erythematosus obsd. in patients treated with the drug. The objective of the present study was to characterize major cytochrome P 450 isoenzyme(s) involved in the N-hydroxylation of procainamide. Firstly, incubations were performed with microsomes from either lymphoblastoid cells or yeast transfected with cDNA encoding for specific human cytochrome P 450 isoenzymes. Expts. performed with these enzyme expression systems indicated that the highest formation rate of N-hydroxyprocainamide was obsd. in the presence of CYP2D6 enriched microsomes. Addnl. expts. demonstrated that the formation rate of N-hydroxyprocainamide by CYP2D6 enriched microsomes was decreased from 45% to 93% by quinidine at concns. ranging from 30 nM to 100 .mu.M (all vs. control) and by approx. 75% by antibodies directed against CYP2D6. Secondly, incubations were performed with microsomes prepd. from 15 human liver samples. Using this approach, an excellent correlation was obsd. between the formation rate of N-hydroxyprocainamide and dextromethorphan O-demethylase activity (CYP2D6: r = 0.9305). In contrast, no correlation could be established between N-hydroxyprocainamide formation rate and caffeine N3-demethylase (CYP1A2), **coumarin** 7-hydroxylase (CYP2A6), S-mephenytoin N-demethylase (**CYP2B6**), tolbutamide methylhydroxylase (CYP2C9), S-mephenytoin 4'-hydroxylase (CYP2C19), chlorzoxazone 6-hydroxylase (CYP2E1), dextromethorphan N-demethylase (CYP3A4), testosterone 6.beta.-hydroxylase (CYP3A4/5) or lauric acid 12-hydroxylase (CYP4A11) activities. Furthermore, formation rate of N-hydroxyprocainamide was decreased in a concn.-dependent manner by quinidine (300 nM to 100 .mu.M) and by antibodies directed against CYP2D6 but not by furafylline 20 .mu.M (CYP1A2), ketoconazole 1 .mu.M (CYP3A4), sulfaphenazole 10 .mu.M (CYP2C9) or antibodies directed against CYP1A1/1A2, CYP2C, CYP2A6, CYP2E1 or CYP3A4/3A5. In conclusion, the results obtained in the present study demonstrate that CYP2D6 is the major human cytochrome P 450 isoenzyme involved in the formation of the reactive metabolite of procainamide, namely N-hydroxyprocainamide.

ACCESSION NUMBER: 1997:705712 CAPLUS
DOCUMENT NUMBER: 127:341363
TITLE: Role of CYP2D6 in the N-hydroxylation of procainamide
AUTHOR(S): Lessard, Etienne; Fortin, Anne; Belanger, Pierre Maxime; Beaune, Philippe; Hamelin, Bettina A.; Turgeon, Jacques
CORPORATE SOURCE: Quebec Heart Institute, Laval Hospital and Faculty of Pharmacy, Laval University, Ste-Foy, PQ, G1V 4G5, Can.
SOURCE: Pharmacogenetics (**1997**), 7(5), 381-390
CODEN: PHMCEE; ISSN: 0960-314X
PUBLISHER: Chapman & Hall
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Pharmacogenetics (**1997**), 7(5), 381-390
CODEN: PHMCEE; ISSN: 0960-314X

AB Sequential oxidns. at the arylamine moiety of the procainamide mol. leading to the formation of N-hydroxyprocainamide and its nitroso deriv. may be responsible for lupus erythematosus obsd. in patients treated with the drug. The objective of the present study was to characterize major cytochrome P 450 isoenzyme(s) involved in the N-hydroxylation of procainamide. Firstly, incubations were performed with microsomes from either lymphoblastoid cells or yeast transfected with cDNA encoding for specific human cytochrome P 450 isoenzymes. Expts. performed with these enzyme expression systems indicated that the highest formation rate of N-hydroxyprocainamide was obsd. in the presence of CYP2D6 enriched microsomes. Addnl. expts. demonstrated that the formation rate of N-hydroxyprocainamide by CYP2D6 enriched microsomes was decreased from 45%

to 93% by quinidine at concns. ranging from 30 nM to 100 .mu.M (all vs. control) and by approx. 75% by antibodies directed against CYP2D6. Secondly, incubations were performed with microsomes prepd. from 15 human liver samples. Using this approach, an excellent correlation was obsd. between the formation rate of N-hydroxyprocainamide and dextromethorphan O-demethylase activity (CYP2D6: r = 0.9305). In contrast, no correlation could be established between N-hydroxyprocainamide formation rate and caffeine N3-demethylase (CYP1A2), **coumarin** 7-hydroxylase (CYP2A6), S-mephenytoin N-demethylase (**CYP2B6**), tolbutamide methylhydroxylase (CYP2C9), S-mephenytoin 4'-hydroxylase (CYP2C19), chlorzoxazone 6-hydroxylase (CYP2E1), dextromethorphan N-demethylase (CYP3A4), testosterone 6.beta.-hydroxylase (CYP3A4/5) or lauric acid 12-hydroxylase (CYP4A11) activities. Furthermore, formation rate of N-hydroxyprocainamide was decreased in a concn.-dependent manner by quinidine (300 nM to 100 .mu.M) and by antibodies directed against CYP2D6 but not by furafylline 20 .mu.M (CYP1A2), ketoconazole 1 .mu.M (CYP3A4), sulfaphenazole 10 .mu.M (CYP2C9) or antibodies directed against CYP1A1/1A2, CYP2C, CYP2A6, CYP2E1 or CYP3A4/3A5. In conclusion, the results obtained in the present study demonstrate that CYP2D6 is the major human cytochrome P 450 isoenzyme involved in the formation of the reactive metabolite of procainamide, namely N-hydroxyprocainamide.

IT 39401-02-0, **Coumarin** 7-hydroxylase 78783-57-0, Lauric acid 12-hydroxylase 95576-27-5 96779-46-3, S-Mephenytoin 4'-hydroxylase 109740-76-3, Dextromethorphan O-demethylase 129553-85-1, Caffeine N3-demethylase 133555-65-4, Metoprolol .alpha.-hydroxylase 135560-20-2, Chlorzoxazone 6-hydroxylase
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(role of cytochrome P 450 isoenzymes and CYP2D6 in the N-hydroxylation of procainamide)

L31 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2002 ACS

AB RP 73401 is a potent inhibitor of cyclic nucleotide phosphodiesterase type IV. RP 73401 is metabolized by human liver microsomes almost exclusively by trans-hydroxylation of the cyclopentyl group to RPR 113406. Liq. chromatog./mass spectrometry/mass spectrometry anal. of plasma from patients given RP 73401 also revealed a mol. ion and fragmentation consistent with RPR 113406. Thus, the objective was to det. the oxidative enzyme(s) responsible for RP 73401 hydroxylation. Kinetic consts. of RP 113406 formation ranged from 8 to 26 .mu.M and 0.83 to 5.99 nmol/min/mg protein for Km and Vmax, resp. Enzyme activity varied 23-fold among 15 human liver microsome samples and correlated with CYP2A6-catalyzed **coumarin** hydroxylase (r2 = 0.85) and **CYP2B6**-catalyzed 7-ethoxytrifluoromethylcoumarin O-deethylase (r2 = 0.82) activities. Chem. inhibition studies showed a 63% decrease in RP 73401 hydroxylation by 500 .mu.M orphenadrine. **Coumarin** (10 .mu.M), however, did not inhibit RP 73401 hydroxylation. Also, anti-CYP2B1 IgG produced 85% inhibition of RP 73401 hydroxylation, but only a negligible decline in **coumarin** hydroxylase activity. Of the 10 expressed P 450 forms studied, only **CYP2B6** catalyzed RP 73401 hydroxylation. Finally, expressed **CYP2B6** showed a high affinity (Km = 22.5 .mu.M) for RP 73401 hydroxylation, similar to the human liver microsome studies.

ACCESSION NUMBER: 1997:645668 CAPLUS
DOCUMENT NUMBER: 127:325908
TITLE: Human liver **CYP2B6**-catalyzed hydroxylation of RP 73401
AUTHOR(S): Stevens, Jeffrey C.; White, Rebecca B.; Hsu, Shih Hsein; Martinet, Michel

CORPORATE SOURCE: Department of Drug Metabolism and Pharmacokinetics, Rhone-Poulenc Rorer, Collegeville, PA, USA
SOURCE: J. Pharmacol. Exp. Ther. (**1997**), 282(3), 1389-1395
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Human liver **CYP2B6**-catalyzed hydroxylation of RP 73401

SO J. Pharmacol. Exp. Ther. (**1997**), 282(3), 1389-1395
CODEN: JPETAB; ISSN: 0022-3565

AB RP 73401 is a potent inhibitor of cyclic nucleotide phosphodiesterase type IV. RP 73401 is metabolized by human liver microsomes almost exclusively by trans-hydroxylation of the cyclopentyl group to RPR 113406. Liq. chromatog./mass spectrometry/mass spectrometry anal. of plasma from patients given RP 73401 also revealed a mol. ion and fragmentation consistent with RPR 113406. Thus, the objective was to det. the oxidative enzyme(s) responsible for RP 73401 hydroxylation. Kinetic consts. of RP 113406 formation ranged from 8 to 26 .mu.M and 0.83 to 5.99 nmol/min/mg protein for Km and Vmax, resp. Enzyme activity varied 23-fold among 15 human liver microsome samples and correlated with CYP2A6-catalyzed **coumarin** hydroxylase (r2 = 0.85) and **CYP2B6**-catalyzed 7-ethoxytrifluoromethylcoumarin O-deethylase (r2 = 0.82) activities. Chem. inhibition studies showed a 63% decrease in RP 73401 hydroxylation by 500 .mu.M orphenadrine. **Coumarin** (10 .mu.M), however, did not inhibit RP 73401 hydroxylation. Also, anti-CYP2B1 IgG produced 85% inhibition of RP 73401 hydroxylation, but only a negligible decline in **coumarin** hydroxylase activity. Of the 10 expressed P 450 forms studied, only **CYP2B6** catalyzed RP 73401 hydroxylation. Finally, expressed **CYP2B6** showed a high affinity (Km = 22.5 .mu.M) for RP 73401 hydroxylation, similar to the human liver microsome studies.

ST liver **CYP2B6** RP 73401 hydroxylation

IT 9035-51-2, Cytochrome P 450, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**CYP2B6**; human liver **CYP2B6**-catalyzed hydroxylation of RP 73401)

IT 144035-83-6, RP 73401
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(human liver **CYP2B6**-catalyzed hydroxylation of RP 73401)

IT 197867-10-0, RPR 113406
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(human liver **CYP2B6**-catalyzed hydroxylation of RP 73401)

L31 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2002 ACS

AB The level of expression and interindividual variation in human hepatic microsomal cytochrome P 450 (CYP) 2B6 was characterized using a polyclonal antibody (WB-2B6) raised against rat CYP2B1. Immunoblot anal. using cDNA-expressed human CYPs revealed strong cross-reactivity of this antibody with **CYP2B6** (limit of detection < 0.05 pmol) and only minor cross-reactivities with human CYP2A6, CYP2D6, and CYP2E1, all of which could be resolved from **CYP2B6** by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Anal. of human liver microsomes using this antibody revealed immunodetectable **CYP2B6** protein in a majority of individual liver samples, with levels up to 74 pmol/mg protein in the **CYP2B6**-pos. samples. Kinetic anal. of cDNA-expressed CYPs identified many of these enzymes as catalysts of

7-ethoxy-4-trifluoromethylcoumarin (7EFC) O-deethylation, but with significantly different apparent KM values (CYP1A2 < **CYP2B6** .apprx. CYP1A1 < CYP2C19 < CYP2C9 < CYP2E1 < CYP2A6). By assaying liver microsomal 7EFC O-deethylase activity at a low 7EFC concn. (5 .mu.M) and preincubating human liver microsomes with anti-CYP1A, anti-CYP2C, and anti-CYP2E1 antibodies, the authors were able to monitor **CYP2B6** -dependent 7EFC O-deethylase activity in a panel of 17 human liver microsomes and observe a significant correlation (r2 = 0.80) between this activity and **CYP2B6** protein content. The ability of **CYP2B6** to activate prodrugs and procarcinogens was examd. using gene locus mutation assays in **CYP2B6**-expressing human lymphoblast cells. **CYP2B6**-expressing cells were found to be more sensitive than control cells to the cytotoxicity and mutagenicity of cyclophosphamide, aflatoxin B1, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. **CYP2B6** is thus a widely expressed human liver microsomal CYP that can contribute to a broad range of drug metab. and procarcinogen activation reactions.

ACCESSION NUMBER: 1997:545509 CAPLUS
DOCUMENT NUMBER: 127:230522
TITLE: Human cytochrome P4502B6. Interindividual hepatic expression, substrate specificity, and role in procarcinogen activation
AUTHOR(S): Code, Erin L.; Crespi, Charles L.; Penman, Bruce W.; Gonzalez, Frank J.; Chang, Thomas K. H.; Waxman, David J.
CORPORATE SOURCE: GENTEST Corporation, Woburn, MA, 01801, USA
SOURCE: Drug Metab. Dispos. (**1997**), 25(8), 985-993
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Drug Metab. Dispos. (**1997**), 25(8), 985-993
CODEN: DMDSAI; ISSN: 0090-9556
AB The level of expression and interindividual variation in human hepatic microsomal cytochrome P 450 (CYP) 2B6 was characterized using a polyclonal antibody (WB-2B6) raised against rat CYP2B1. Immunoblot anal. using cDNA-expressed human CYPs revealed strong cross-reactivity of this antibody with **CYP2B6** (limit of detection < 0.05 pmol) and only minor cross-reactivities with human CYP2A6, CYP2D6, and CYP2E1, all of which could be resolved from **CYP2B6** by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Anal. of human liver microsomes using this antibody revealed immunodetectable **CYP2B6** protein in a majority of individual liver samples, with levels up to 74 pmol/mg protein in the **CYP2B6**-pos. samples. Kinetic anal. of cDNA-expressed CYPs identified many of these enzymes as catalysts of 7-ethoxy-4-trifluoromethylcoumarin (7EFC) O-deethylation, but with significantly different apparent KM values (CYP1A2 < **CYP2B6** .apprx. CYP1A1 < CYP2C19 < CYP2C9 < CYP2E1 < CYP2A6). By assaying liver microsomal 7EFC O-deethylase activity at a low 7EFC concn. (5 .mu.M) and preincubating human liver microsomes with anti-CYP1A, anti-CYP2C, and anti-CYP2E1 antibodies, the authors were able to monitor **CYP2B6** -dependent 7EFC O-deethylase activity in a panel of 17 human liver microsomes and observe a significant correlation (r2 = 0.80) between this activity and **CYP2B6** protein content. The ability of **CYP2B6** to activate prodrugs and procarcinogens was examd. using gene locus mutation assays in **CYP2B6**-expressing human lymphoblast cells. **CYP2B6**-expressing cells were found to be more sensitive than control cells to the cytotoxicity and mutagenicity of

cyclophosphamide, aflatoxin B1, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. **CYP2B6** is thus a widely expressed human liver microsomal CYP that can contribute to a broad range of drug metab. and procarcinogen activation reactions.

IT 39401-02-0, **Coumarin** 7-hydroxylase 42613-26-3, 7-Ethoxycoumarin O-deethylase 67724-61-2, Phenacetin O-deethylase 96779-46-3, (S)-Mephenytoin 4'-hydroxylase 126341-87-5, p-Nitrophenol hydroxylase 146359-59-3, Diclofenac 4'-hydroxylase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(human cytochrome P 4502B6 - interindividual hepatic expression, substrate specificity, and role in procarcinogen activation)

L31 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2002 ACS

AB 7-Ethoxy-4-trifluoromethylcoumarin (7-EFC) was examd. as a substrate for cytochrome P 450 (P 450) in microsomes from human livers and expressed in B-lymphoblastoid cells. The O-deethylation of 7-EFC to 7-hydroxy-4-trifluoromethylcoumarin (7-HFC) varied over a liver bank by a factor of 13 (40-507 pmol min-1mg-1 protein). When compared with the ability of the bank of human liver samples to metabolize form-selective substrates of the P 450, 7-HFC formation correlated strongly with the formation of the S-mephenytoin metabolite, nirvanol (r2 = 0.86). .alpha.-Naphthoflavone (ANF), diethyldithiocarbamate (DDC) and chloramphenicol (CAP) inhibited the O-deethylation of 7-EFC by microsomes from human livers by greater than 60%. Orphenadrine (ORP), a reported specific **CYP2B6** inhibitor, was a less potent inhibitor of 7-HFC formation by microsomes from human liver than DDC or ANF. Using microsomes from B-lymphoblastoid cells expressing specific P450s, **CYP2B6** and CYP1A2 were found to produce substantial levels of 7-HFC whereas CYP2E1 and CYP2C19 produced detectable amts. of this metabolite. ORP inhibited expressed CYP2E1 and **CYP2B6** mediated 7-HFC formation to a greater extent than the inhibition obsd. for CYP1A2. Methoxychlor and S-mephenytoin inhibited expressed **CYP2B6** but not CYP1A2 mediated 7-EFC O-deethylation. Livers with high relative rates of 7-HFC formation displayed biphasic enzyme kinetics with the low Km site (av. Km = 3.3 .mu.M) demonstrating allosteric activation. Five livers with low relative rates of 7-HFC formation also exhibited biphasic kinetics but lacked evidence of an allosteric mechanism being involved in the low Km component (av. Km = 2.4 .mu.M). Furthermore, expressed **CYP2B6** and CYP2E1 converted 7-EFC to 7-HFC with allosteric activation indicated, while CYP1A2 mediated metab. of 7-EFC to 7-HFC best fit the classic Michaelis-Menten model. A com. available antibody to rat CYP2B, suggested to be specific for **CYP2B6**, was found to cross react with all members of the CYP2 family examd. including CYP2C19, which possessed a nearly identical electrophoretic mobility to that of **CYP2B6** in the system examd. In total, the evidence presented indicates that multiple P450s are involved in the formation of 7-HFC from 7-EFC, therefore this does not appear to be a useful or a selective probe of **CYP2B6** catalytic activity. Furthermore, the specificity of both antibody and chem. inhibitor (ORP) probes previously suggested to be specific for **CYP2B6** is also questioned.

ACCESSION NUMBER: 1997:498564 CAPLUS
DOCUMENT NUMBER: 127:187361
TITLE: Examination of purported probes of human **CYP2B6**
AUTHOR(S): Ekins, Sean; VandenBranden, Mark; Ring, Barbara J.; Wrighton, Steven A.
CORPORATE SOURCE: Department of Drug Disposition, Lilly Research

Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, 46285, USA
SOURCE: Pharmacogenetics (1997), 7(3), 165-179
CODEN: PHMCEE; ISSN: 0960-314X
PUBLISHER: Chapman & Hall
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Examination of purported probes of human **CYP2B6**

SO Pharmacogenetics (1997), 7(3), 165-179
CODEN: PHMCEE; ISSN: 0960-314X

AB 7-Ethoxy-4-trifluoromethylcoumarin (7-EFC) was examd. as a substrate for cytochrome P 450 (P 450) in microsomes from human livers and expressed in B-lymphoblastoid cells. The O-deethylation of 7-EFC to 7-hydroxy-4-trifluoromethylcoumarin (7-HFC) varied over a liver bank by a factor of 13 (40-507 pmol min-1mg-1 protein). When compared with the ability of the bank of human liver samples to metabolize form-selective substrates of the P 450, 7-HFC formation correlated strongly with the formation of the S-mephenytoin metabolite, nirvanol (r2 = 0.86). .alpha.-Naphthoflavone (ANF), diethyldithiocarbamate (DDC) and chloramphenicol (CAP) inhibited the O-deethylation of 7-EFC by microsomes from human livers by greater than 60%. Orphenadrine (ORP), a reported specific **CYP2B6** inhibitor, was a less potent inhibitor of 7-HFC formation by microsomes from human liver than DDC or ANF. Using microsomes from B-lymphoblastoid cells expressing specific P450s, **CYP2B6** and CYP1A2 were found to produce substantial levels of 7-HFC whereas CYP2E1 and CYP2C19 produced detectable amts. of this metabolite. ORP inhibited expressed CYP2E1 and **CYP2B6** mediated 7-HFC formation to a greater extent than the inhibition obsd. for CYP1A2. Methoxychlor and S-mephenytoin inhibited expressed **CYP2B6** but not CYP1A2 mediated 7-EFC O-deethylation. Livers with high relative rates of 7-HFC formation displayed biphasic enzyme kinetics with the low Km site (av. Km = 3.3 .mu.M) demonstrating allosteric activation. Five livers with low relative rates of 7-HFC formation also exhibited biphasic kinetics but lacked evidence of an allosteric mechanism being involved in the low Km component (av. Km = 2.4 .mu.M). Furthermore, expressed **CYP2B6** and CYP2E1 converted 7-EFC to 7-HFC with allosteric activation indicated, while CYP1A2 mediated metab. of 7-EFC to 7-HFC best fit the classic Michaelis-Menten model. A com. available antibody to rat CYP2B, suggested to be specific for **CYP2B6**, was found to cross react with all members of the CYP2 family examd. including CYP2C19, which possessed a nearly identical electrophoretic mobility to that of **CYP2B6** in the system examd. In total, the evidence presented indicates that multiple P450s are involved in the formation of 7-HFC from 7-EFC, therefore this does not appear to be a useful or a selective probe of **CYP2B6** catalytic activity. Furthermore, the specificity of both antibody and chem. inhibitor (ORP) probes previously suggested to be specific for **CYP2B6** is also questioned.

ST cytochrome P450 **CYP2B6** antibody inhibitor specificity

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(anti-CYP2B; examn. of purported probes of human **CYP2B6**)

IT Enzyme kinetics
Liver
(examn. of purported probes of human **CYP2B6**)

IT Proteins (specific proteins and subclasses)
RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); ANST (Analytical

study); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(gene **CYP2B6**; examn. of purported probes of human **CYP2B6**)

IT 56-54-2, Quinidine 56-75-7, CAP 83-98-7, ORP 91-64-5, **Coumarin** 147-84-2, DDC, biological studies 526-08-9, Sulphaphenazole 604-59-1, ANF 2751-09-9, TAO 70989-04-7, S-Mephenytoin 80288-49-9, Furafylline
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(examn. of purported probes of human **CYP2B6**)

IT 9035-51-2, Cytochrome P 450, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(examn. of purported probes of human **CYP2B6**)

IT 115453-82-2, 7-Ethoxy-4-trifluoromethylcoumarin
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(examn. of purported probes of human **CYP2B6**)

IT 575-03-1, 7-Hydroxy-4-trifluoromethylcoumarin
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(examn. of purported probes of human **CYP2B6**)

L31 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2002 ACS

AB An improved method for measuring the activity of a promoter sequence in a mammalian cell using a reporter gene is provided. Expression can be measured at low levels using fluorometric assay systems based on the hydroxylation of **coumarins**. The improvement involves using a reporter cassette contg. a DNA sequence encoding a cytochrome P 450 with a polyadenylation signal sequence as the reporter gene. Compns. contg. the cytochrome P 450 reporter cassette also are provided. Construction of core expression cassettes that give stable expression is described. The first expression constructs were sensitive to DNA methylation and were modified to remove methylatable sequences.

ACCESSION NUMBER: 1997:251154 CAPLUS
DOCUMENT NUMBER: 126:234425
TITLE: A cytochrome P450 reporter gene for assay of promoter function in mammalian cells
INVENTOR(S): Crespi, Charles L.; Penman, Bruce W.; Gonzales, Frank J.; Gelboin, Harry V.; Sher, Talia
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA; Gentest Corporation
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9708342	A1	19970306	WO 1996-US13622	19960822 <--

W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: US 1995-2947P P 19950830
PI WO 9708342 A1 **19970306**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9708342	A1	19970306	WO 1996-US13622	19960822 <--

W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

AB An improved method for measuring the activity of a promoter sequence in a mammalian cell using a reporter gene is provided. Expression can be measured at low levels using fluorometric assay systems based on the hydroxylation of **coumarins**. The improvement involves using a reporter cassette contg. a DNA sequence encoding a cytochrome P 450 with a polyadenylation signal sequence as the reporter gene. Compns. contg. the cytochrome P 450 reporter cassette also are provided. Construction of core expression cassettes that give stable expression is described. The first expression constructs were sensitive to DNA methylation and were modified to remove methylatable sequences.

IT Genes (animal)
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**CYP2B6**, as reporter; cytochrome P 450 reporter gene for assay of promoter function in mammalian cells)

IT 91-64-5D, **Coumarin**, substituted analogs 607-71-6, 4-Methylcoumarin 607-71-6D, 4-Methylcoumarin, 7-alkoxy derivs. 635-78-9D, Resorufin, substituted analogs, 7-alkoxy derivs. 1916-63-8D, Phenoxazin-3-one, substituted analogs 15119-34-3, 3-Cyanocoumarin 15119-34-3D, 3-Cyanocoumarin, 7-alkoxy derivs. 151191-43-4 151191-43-4D, 7-alkoxy derivs.
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(as cytochrome P 450 assay substrate; cytochrome P 450 reporter gene for assay of promoter function in mammalian cells)

L31 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2002 ACS

AB In vitro methods were used to identify the cytochrome P 450 (CYP) enzyme(s) involved in S-mephenytoin N-demethylation. S-mephenytoin (200 .mu.M) was incubated with human liver microsomes, and nirvanol formation was quantitated by reversed-phase HPLC. Mephenytoin N-demethylase activity in a panel of human liver microsomes ranged 35-fold from 9 to 319 pmol/min protein and correlated strongly with microsomal **CYP2B6** activity (r = 0.91). Addnl. correlation were found with microsomal CYP2A6 and CYP3A4 activity (r = 0.88 and 0.74, resp.). Microsomes prepd. from human .beta.-lymphoblastoid cells transformed with individual P 450 cDNAs were assayed for S-mephenytoin N-demethylase activity. Of 11 P 450 isoforms (P450s 1A1, 1A2, 2A6, 2B6, 2E1, 2D6, 2C8, 2C9, 3A4, and 3A5) tested, only **CYP2B6** catalyzed the N-demethylation of S-mephenytoin with an apparent Km of 564 .mu.M. Expts. with P 450 form-selective chem. inhibitors, competitive substrates, and anti-P 450 antibodies were also performed. Troleandomycin, a mechanism-based CYP3A selective inhibitor, and **coumarin**, a substrate for CYP2A6 and therefore a potential competitive inhibitor, failed to inhibit human liver microsomal S-mephenytoin N-demethylation. In contrast, orphenadrine, an inhibitor of CYP2B forms, produced at 51.OMEGA.4% decrease in S-mephenytoin N-demethylase activity in human liver microsomes and a 45% decrease in recombinant microsomes expressing **CYP2B6**. Also, both **CYP2B6**-marker 7-ethoxytrifluoromethylcoumarin O-deethylase and S-mephenytoin N-demethylase activities were inhibited by .apprx.65% by 5 mg anti-CYP2B1 IgG/mg microsomal protein. Finally, polyclonal antibody inhibitory to CYP3A1 failed to inhibit S-mephenytoin N-demethylase activity. Taken together, these studies indicate that the N-demethylation of S-mephenytoin by human liver microsomes is catalyzed primarily by **CYP2B6**.

ACCESSION NUMBER: 1996:589147 CAPLUS
DOCUMENT NUMBER: 125:264890

TITLE: Catalytic role of cytochrome P4502B6 in the N-demethylation of S-mephenytoin
AUTHOR(S): Heyn, Heleen; White, Rebecca B.; Stevens, Jeffrey C.
CORPORATE SOURCE: Dep. Drug Metab. Pharmacokinetics, Rhone-Poulenc Rorer Res. Development, Collegeville, PA, 19426-0107, USA
SOURCE: Drug Metab. Dispos. (**1996**), 24(9), 948-954
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Drug Metab. Dispos. (**1996**), 24(9), 948-954
CODEN: DMDSAI; ISSN: 0090-9556
AB In vitro methods were used to identify the cytochrome P 450 (CYP) enzyme(s) involved in S-mephenytoin N-demethylation. S-mephenytoin (200 .mu.M) was incubated with human liver microsomes, and nirvanol formation was quantitated by reversed-phase HPLC. Mephenytoin N-demethylase activity in a panel of human liver microsomes ranged 35-fold from 9 to 319 pmol/min protein and correlated strongly with microsomal **CYP2B6** activity (r = 0.91). Addnl. correlation were found with microsomal CYP2A6 and CYP3A4 activity (r = 0.88 and 0.74, resp.). Microsomes prepd. from human .beta.-lymphoblastoid cells transformed with individual P 450 cDNAs were assayed for S-mephenytoin N-demethylase activity. Of 11 P 450 isoforms (P450s 1A1, 1A2, 2A6, 2B6, 2E1, 2D6, 2C8, 2C9, 3A4, and 3A5) tested, only **CYP2B6** catalyzed the N-demethylation of S-mephenytoin with an apparent Km of 564 .mu.M. Expts. with P 450 form-selective chem. inhibitors, competitive substrates, and anti-P 450 antibodies were also performed. Troleandomycin, a mechanism-based CYP3A selective inhibitor, and **coumarin**, a substrate for CYP2A6 and therefore a potential competitive inhibitor, failed to inhibit human liver microsomal S-mephenytoin N-demethylation. In contrast, orphenadrine, an inhibitor of CYP2B forms, produced at 51.OMEGA.4% decrease in S-mephenytoin N-demethylase activity in human liver microsomes and a 45% decrease in recombinant microsomes expressing **CYP2B6**. Also, both **CYP2B6**-marker 7-ethoxytrifluoromethylcoumarin O-deethylase and S-mephenytoin N-demethylase activities were inhibited by .apprx.65% by 5 mg anti-CYP2B1 IgG/mg microsomal protein. Finally, polyclonal antibody inhibitory to CYP3A1 failed to inhibit S-mephenytoin N-demethylase activity. Taken together, these studies indicate that the N-demethylation of S-mephenytoin by human liver microsomes is catalyzed primarily by **CYP2B6**.

L31 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2002 ACS
AB We evaluated the specificity of 15 substrates and 14 inhibitors of the cytochrome P450s using nine human P 450 isoforms expressed in HepG2 cells using a recombinant vaccinia virus and also in human liver microsomes. **Coumarin**, 7-ethoxyresorufin, 7-benzyloxyresorufin, tolbutamide, aniline and diazepam were isoform-selective substrates towards CYP2A6, the CYP1A subfamily, **CYP2B6**, the CYP2C subfamily, CYP2E1 and the CYP3A subfamily, resp. However, a selective substrate for CYP2D6 was not found among the chems. tested. SKF-525A inhibited > 40% of the metabolic activity of all substrates tested, and the inhibitory effects differed among P 450 isoforms. Sulfaphenazole, 7,8-benzoflavone, quinidine and troleandomycin were selective inhibitors of the CYP2C subfamily (except CYP2C19), the CYP1A subfamily, CYP2D6 and the CYP3A subfamily, resp. Methoxsalen (CYP2A6 inhibitor) inhibited the metabolic activity of CYP1A2 as well as that of CYP2A6. Diethyldithiocarbamate (CYP2E1 inhibitor) inhibited the metabolic activities of CYP2A6 and CYP2C19 in addn. to that of CYP2E1. Our results indicated that substrates and inhibitors reported as P 450 selective probes are not necessarily specific for individual

human P 450 isoforms. These results may provide useful information regarding human P 450 substrates and inhibitors in vitro using human liver microsomal samples.

ACCESSION NUMBER: 1996:424712 CAPLUS
DOCUMENT NUMBER: 125:80284
TITLE: Specificity of substrate and inhibitor probes for cytochrome P450s: evaluation of in vitro metabolism using cDNA-expressed human P450s and human liver microsomes
AUTHOR(S): Ono, S.; Hatanaka, T.; Hotta, H.; Satoh, T.; Gonzalez, F. J.; Tsutsui, M.
CORPORATE SOURCE: Amersham K.K., Central Lab. for Research and Development, Chiba, 270-14, Japan
SOURCE: Xenobiotica (**1996**), 26(7), 681-693
CODEN: XENOBH; ISSN: 0049-8254
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Xenobiotica (**1996**), 26(7), 681-693
CODEN: XENOBH; ISSN: 0049-8254

AB We evaluated the specificity of 15 substrates and 14 inhibitors of the cytochrome P450s using nine human P 450 isoforms expressed in HepG2 cells using a recombinant vaccinia virus and also in human liver microsomes. **Coumarin**, 7-ethoxyresorufin, 7-benzyloxyresorufin, tolbutamide, aniline and diazepam were isoform-selective substrates towards CYP2A6, the CYP1A subfamily, **CYP2B6**, the CYP2C subfamily, CYP2E1 and the CYP3A subfamily, resp. However, a selective substrate for CYP2D6 was not found among the chems. tested. SKF-525A inhibited > 40% of the metabolic activity of all substrates tested, and the inhibitory effects differed among P 450 isoforms. Sulfaphenazole, 7,8-benzoflavone, quinidine and troleandomycin were selective inhibitors of the CYP2C subfamily (except CYP2C19), the CYP1A subfamily, CYP2D6 and the CYP3A subfamily, resp. Methoxsalen (CYP2A6 inhibitor) inhibited the metabolic activity of CYP1A2 as well as that of CYP2A6. Diethyldithiocarbamate (CYP2E1 inhibitor) inhibited the metabolic activities of CYP2A6 and CYP2C19 in addn. to that of CYP2E1. Our results indicated that substrates and inhibitors reported as P 450 selective probes are not necessarily specific for individual human P 450 isoforms. These results may provide useful information regarding human P 450 substrates and inhibitors in vitro using human liver microsomal samples.

IT 9012-80-0, Aniline 4-hydroxylase 39401-02-0, **Coumarin** 7-hydroxylase 59793-97-4, 7-Ethoxyresorufin O-deethylase 84067-35-6, Diazepam 3-hydroxylase 85204-91-7, 7-Benzyloxyresorufin O-debenzylase 94949-24-3, Bufuralol 1'-hydroxylase 96779-46-3, S-Mephenytoin 4'-hydroxylase 106527-94-0, Tolbutamide methyl-hydroxylase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(cytochrome P 450-dependent; specificity of substrate and inhibitor probes for cytochrome P 450 isoforms)

IT 57-41-0, Phenytoin 58-08-2, Caffeine, biological studies 58-22-0, Testosterone 58-55-9, Theophylline, biological studies 62-53-3, Aniline, biological studies 64-77-7, Tolbutamide 91-64-5, **Coumarin** 95-25-0, Chlorzoxazone 125-71-3, Dextromethorphan 439-14-5, Diazepam 5725-91-7, 7-Ethoxyresorufin 54340-62-4, Bufuralol 70989-04-7, S-Mephenytoin 87687-02-3, 7-Benzyloxyresorufin 87687-03-4, Pentoxyresorufin
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(specificity of substrate and inhibitor probes for cytochrome P 450 isoforms)

L31 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2002 ACS

AB The oxidn. of O6-benzylguanine, an inactivator of O6-alkylguaine-DNA alkyltransferase, was examd. using human liver cytosol, microsomes, and several P 450 isoforms. Incubation of O6-benzylguanine with human liver cytosol resulted in the formation of O6-benzyl-8-oxoguanine, which was inhibited by **menadione**, a potent inhibitor of aldehyde oxidase. Inhibition by allopurinol, a xanthine oxidase inhibitor, was less dramatic. Oxidn. of O6-benzylguanine also occurred with pooled human liver microsomes and was inhibited by both furafylline and troleandomycin, selective inhibitors of CYPIA2 and CYP3A4, resp. Human P450s, CYPIA2, **CYP2B6**, CYP2C8, CYP2C9, CYP2E1, and CYP3A4 expressed in Hep G2 hepatoma cells using vaccinia virus vectors were incubated with 10 or 200 .mu.M O6-benzylguanine. At 10 .mu.M, O6-benzylguanine was oxidized primarily by CYP1A2 and to a lesser extent by CYP3A4. However, an appreciable increase in CYP3A4 contribution was noted at 200 .mu.M. CYP1A2 exhibited a more than 200-fold higher relative catalytic activity (Vmax/Km) compared with CYP3A4. Therefore, at therapeutically relevant concns. of O6-benzylguanine, CYP1A2 could be primarily involved in its oxidn. since it shows a much lower Km value (1.3 .mu.M) than CYP3A4 (52.2 .mu.M) and cytosol (81.5 .mu.M). However, one would expect interindividual variation in the extent of oxidn. of O6-benzylguanine depending on the levels of aldehyde oxidase, CYP1A2, and CYP3A4.

ACCESSION NUMBER: 1995:977103 CAPLUS
DOCUMENT NUMBER: 124:44720
TITLE: Human liver oxidative metabolism of O6-benzylguanine
AUTHOR(S): Roy, Sandip K.; Korzekwa, Kenneth R.; Gonzalez, Frank J.; Moschel, Robert C.; Dolan, M. Eileen
CORPORATE SOURCE: Section Hematology-Oncology, Univ. Chicago, Chicago, IL, 60637, USA
SOURCE: Biochem. Pharmacol. (**1995**), 50(9), 1385-9
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Biochem. Pharmacol. (**1995**), 50(9), 1385-9
CODEN: BCPCA6; ISSN: 0006-2952
AB The oxidn. of O6-benzylguanine, an inactivator of O6-alkylguaine-DNA alkyltransferase, was examd. using human liver cytosol, microsomes, and several P 450 isoforms. Incubation of O6-benzylguanine with human liver cytosol resulted in the formation of O6-benzyl-8-oxoguanine, which was inhibited by **menadione**, a potent inhibitor of aldehyde oxidase. Inhibition by allopurinol, a xanthine oxidase inhibitor, was less dramatic. Oxidn. of O6-benzylguanine also occurred with pooled human liver microsomes and was inhibited by both furafylline and troleandomycin, selective inhibitors of CYPIA2 and CYP3A4, resp. Human P450s, CYPIA2, **CYP2B6**, CYP2C8, CYP2C9, CYP2E1, and CYP3A4 expressed in Hep G2 hepatoma cells using vaccinia virus vectors were incubated with 10 or 200 .mu.M O6-benzylguanine. At 10 .mu.M, O6-benzylguanine was oxidized primarily by CYP1A2 and to a lesser extent by CYP3A4. However, an appreciable increase in CYP3A4 contribution was noted at 200 .mu.M. CYP1A2 exhibited a more than 200-fold higher relative catalytic activity (Vmax/Km) compared with CYP3A4. Therefore, at therapeutically relevant concns. of O6-benzylguanine, CYP1A2 could be primarily involved in its oxidn. since it shows a much lower Km value (1.3 .mu.M) than CYP3A4 (52.2 .mu.M) and cytosol (81.5 .mu.M). However, one would expect interindividual variation in the extent of oxidn. of O6-benzylguanine depending on the levels of aldehyde oxidase, CYP1A2, and CYP3A4.

L31 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2002 ACS

AB The present study investigated the role of rat and human cytochrome P 450 enzymes in the sulfoxidn. of S-Me N,N-diethylthiolcarbamate (DETC-Me) to S-Me N,N-diethylthiolcarbamate sulfoxide (DETC-Me sulfoxide), the putative active metabolite of disulfiram. DETC-Me sulfoxidn. by microsomes from male and female rats treated with various cytochrome P 450-enzyme inducers suggested that multiple enzymes can catalyze this reaction, and these include, CYP1A1/2, CYP2B1/2, and CYP3A1/2. All cDNA-expressed human cytochrome P 450 enzymes examd. catalyzed the sulfoxidn. of DETC-Me. The turnover rates (min-1) of DETC-Me sulfoxidn. by the cDNA-expressed cytochrome P 450 enzymes ranked as follows: CYP3A4 > CYP2A6 - CYP2C9 > CYP1A2 > **CYP2B6** - CYP2E1 > CYP1A1 > CYP2D6. Interestingly, CYP3A4 ranked first or last, depending on whether or not addnl. NADPH-cytochrome P 450 reductase was coexpressed in the lymphoblastoid cells. This complicated ests. of the contribution of CYP3A4 to DETC-Me sulfoxidn. by human liver microsomes. The sample-to-sample variation in DETC-Me sulfoxidn. by a bank of human liver microsomes (N = 13) correlated highly with **coumarin** 7-hydroxylation (r = 0.88) and testosterone 6.beta.-hydroxylation (r = 0.90), suggesting that CYP2A6 and CYP3A4/5 contribute to the sulfoxidn. of DETC-Me by human liver microsomes. Although, chlorzoxazone 6-hydroxylation (a marker for CYP2E1) correlated poorly with DETC-Me sulfoxidn., the correlation improved from r = 0.07 to r = 0.44 when DETC-Me sulfoxidn. was studied in the presence of the CYP2A6 inhibitor, **coumarin**. Similarly, when DETC-Me sulfoxidn. was studied in the presence of diethyldithiocarbamate (DDTC), the inhibited DETC-Me sulfoxidase activity correlated better (r = 0.50) with chlorzoxazone 6-hydroxylase, compared with DETC-Me sulfoxidase activity in the absence of DDTC (r = 0.09). Polyclonal antibodies against CYP2E1 caused a modest inhibition (30%) of DETC-Me sulfoxidn. by human liver microsomes. Anti-CYP3A1 antibodies completely inhibited DETC-Me sulfoxidn. by cDNA-expressed CYP3A4. Under similar conditions, DETC-Me sulfoxidn. by human liver microsomes was only partially inhibited by anti-CYP3A1 antibodies. Although studies with the rat and cDNA-expressed cytochrome P 450 enzymes suggested that CYP1A2 contributed to DETC-Me sulfoxidn., this reaction was not inhibited by either furafylline (a mechanism-based inhibitor of CYP1A2) or antibodies against CYP1A1/2. A significant role for CYP2C9 was excluded by the inability of sulfaphenazole to inhibit the sulfoxidn. of DETC-Me by human liver microsomes. Collectively, these data suggest that multiple cytochrome P 450 enzymes can catalyze the sulfoxidn. of DETC-Me. In human liver microsomes the CYP2A6, CYP2E1, and CYP3A4/5 all contribute significantly to the sulfoxidn. of DETC-Me. It is interesting to note that DDTC, the reduced metabolite of disulfiram, is known to inhibit these same enzymes. The ability of DDTC to block the formation of DETC-Me sulfoxide may explain why the dose of disulfiram required to produce a disulfiram-ethanol reaction in alcoholics is so variable and often inadequate.

ACCESSION NUMBER: 1995:895750 CAPLUS
DOCUMENT NUMBER: 123:333330
TITLE: Identification of the human and rat P450 enzymes responsible for the sulfoxidation of S-methyl N,N-diethylthiolcarbamate (DETC-ME): the terminal step in the bioactivation of disulfiram
AUTHOR(S): Madan, Ajay; Parkinson, Andrew; Faiman, Morris D.
CORPORATE SOURCE: Department Pharmacology, Toxicology, University Kansas, Lawrence, KS, 66045, USA
SOURCE: Drug Metab. Dispos. (**1995**), 23(10), 1153-62
CODEN: DMDSAI; ISSN: 0090-9556

DOCUMENT TYPE: Journal
LANGUAGE: English
SO Drug Metab. Dispos. (**1995**), 23(10), 1153-62
CODEN: DMDSAI; ISSN: 0090-9556

AB The present study investigated the role of rat and human cytochrome P 450 enzymes in the sulfoxidn. of S-Me N,N-diethylthiolcarbamate (DETC-Me) to S-Me N,N-diethylthiolcarbamate sulfoxide (DETC-Me sulfoxide), the putative active metabolite of disulfiram. DETC-Me sulfoxidn. by microsomes from male and female rats treated with various cytochrome P 450-enzyme inducers suggested that multiple enzymes can catalyze this reaction, and these include, CYP1A1/2, CYP2B1/2, and CYP3A1/2. All cDNA-expressed human cytochrome P 450 enzymes examd. catalyzed the sulfoxidn. of DETC-Me. The turnover rates (min-1) of DETC-Me sulfoxidn. by the cDNA-expressed cytochrome P 450 enzymes ranked as follows: CYP3A4 > CYP2A6 - CYP2C9 > CYP1A2 > **CYP2B6** - CYP2E1 > CYP1A1 > CYP2D6. Interestingly, CYP3A4 ranked first or last, depending on whether or not addnl. NADPH-cytochrome P 450 reductase was coexpressed in the lymphoblastoid cells. This complicated ests. of the contribution of CYP3A4 to DETC-Me sulfoxidn. by human liver microsomes. The sample-to-sample variation in DETC-Me sulfoxidn. by a bank of human liver microsomes (N = 13) correlated highly with **coumarin** 7-hydroxylation (r = 0.88) and testosterone 6.beta.-hydroxylation (r = 0.90), suggesting that CYP2A6 and CYP3A4/5 contribute to the sulfoxidn. of DETC-Me by human liver microsomes. Although, chlorzoxazone 6-hydroxylation (a marker for CYP2E1) correlated poorly with DETC-Me sulfoxidn., the correlation improved from r = 0.07 to r = 0.44 when DETC-Me sulfoxidn. was studied in the presence of the CYP2A6 inhibitor, **coumarin**. Similarly, when DETC-Me sulfoxidn. was studied in the presence of diethyldithiocarbamate (DDTC), the inhibited DETC-Me sulfoxidase activity correlated better (r = 0.50) with chlorzoxazone 6-hydroxylase, compared with DETC-Me sulfoxidase activity in the absence of DDTC (r = 0.09). Polyclonal antibodies against CYP2E1 caused a modest inhibition (30%) of DETC-Me sulfoxidn. by human liver microsomes. Anti-CYP3A1 antibodies completely inhibited DETC-Me sulfoxidn. by cDNA-expressed CYP3A4. Under similar conditions, DETC-Me sulfoxidn. by human liver microsomes was only partially inhibited by anti-CYP3A1 antibodies. Although studies with the rat and cDNA-expressed cytochrome P 450 enzymes suggested that CYP1A2 contributed to DETC-Me sulfoxidn., this reaction was not inhibited by either furafylline (a mechanism-based inhibitor of CYP1A2) or antibodies against CYP1A1/2. A significant role for CYP2C9 was excluded by the inability of sulfaphenazole to inhibit the sulfoxidn. of DETC-Me by human liver microsomes. Collectively, these data suggest that multiple cytochrome P 450 enzymes can catalyze the sulfoxidn. of DETC-Me. In human liver microsomes the CYP2A6, CYP2E1, and CYP3A4/5 all contribute significantly to the sulfoxidn. of DETC-Me. It is interesting to note that DDTC, the reduced metabolite of disulfiram, is known to inhibit these same enzymes. The ability of DDTC to block the formation of DETC-Me sulfoxide may explain why the dose of disulfiram required to produce a disulfiram-ethanol reaction in alcoholics is so variable and often inadequate.

L31 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2002 ACS

AB Non-tumorigenic, stable, human bronchial and liver epithelial cell lines are provided wherein the cell lines are capable of expressing human cytochrome P 450 genes which have been inserted into the cell lines. Also provided are method of kits for identifying potential mutagens, cytotoxins, carcinogens, chemotherapeutic and chemopreventive agents utilizing these cell lines.

ACCESSION NUMBER: 1995:386284 CAPLUS
DOCUMENT NUMBER: 122:153382
TITLE: Immortalized human cell lines containing exogenous cytochrome p450 genes
INVENTOR(S): Harris, Curtis C.; Gelboin, Harry V.; Gonzalez, Frank J.; Mace, Katharine C.; Pfeifer, Andrea M. A.
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA; Nestec S.A.
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 9426905	A1	19941124	WO 1994-US5472	19940517	<--
W: AU, CA, JP					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
US 5506131	A	19960409	US 1993-65201	19930519	<--
AU 9469145	A1	19941212	AU 1994-69145	19940517	<--
AU 697896	B2	19981022			
EP 700442	A1	19960313	EP 1994-917408	19940517	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					

PRIORITY APPLN. INFO.:

US 1993-65201	A	19930519
US 1987-58387	B2	19870605
US 1987-114508	A2	19871030
US 1988-265883	B2	19881101
US 1991-636712	A2	19910102
US 1991-787777	A2	19911106
US 1992-869818	A2	19920413
WO 1994-US5472	W	19940517

PI WO 9426905 A1 **19941124**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI WO 9426905	A1	19941124	WO 1994-US5472	19940517	<--
W: AU, CA, JP					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
US 5506131	A	19960409	US 1993-65201	19930519	<--
AU 9469145	A1	19941212	AU 1994-69145	19940517	<--
AU 697896	B2	19981022			
EP 700442	A1	19960313	EP 1994-917408	19940517	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					

IT Gene, animal
RL: BPR (Biological process); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(**CYP2B6**; immortalized human cell lines contg. exogenous cytochrome P 450 genes)

IT 9035-51-2P, Cytochrome P 450, analysis 39401-02-0P, **Coumarin** 7-hydroxylase 42613-26-3P, Ethoxycoumarin deethylase 59793-97-4P, Ethoxyresorufin O-deethylase
RL: ARU (Analytical role, unclassified); BPN (Biosynthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation)
(immortalized human cell lines contg. exogenous cytochrome P 450 genes)

L31 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2002 ACS
AB Short-chain satd. halocarbons, including isoflurane and the

chlorofluorocarbon substitute HCFC-123, can strongly potentiate the cytochrome P 450-dependent oxidn. of gaseous haloethenes, such as 2-chloro-1,1-difluoroethene (CDE) and vinyl chloride, in vivo and in vitro. P 450 isoenzyme specificity in this effect is suggested by the fact that the interaction is pronounced in microsomes from rats treated with phenobarbital, but does not occur in microsomes of isoniazid- or .beta.-naphthoflavone-treated animals. The authors examd. the effect of isoflurane on CDE defluorination in liver microsomes from 10 human organ donors to det. whether satd. halocarbon/haloethene interactions also occur in humans and, if so, to det. the cytochromes P 450 involved. Three of the samples exhibited isoflurane-stimulated increases (24, 32, and 41%) in CDE defluorination; isoflurane either inhibited or had no effect on CDE metab. in the other seven samples. Two samples in which isoflurane potentiated CDE metab. to the greatest rates had higher **coumarin** 7-hydroxylase (indicative of CYP2A6), 7-ethoxycoumarin O-deethylase (**CYP2B6**), and nifedipine oxidase (CYP3A4) activities than the other eight samples. However, all 10 subjects had similar rates of phenacetin O-deethylation (CYP1A2) and chlorzoxazone 6-hydroxylation (CYP2E1). In microsomes from cells transfected with cDNAs coding for individual human P450s, CDE metab. by **CYP2B6** was stimulated (216%) by isoflurane, whereas isoflurane did not stimulate CDE metab. by human CYP2A6, CYP3A4, CYP2D6, or CYP2E1. Isoflurane highly increased CDE defluorination in purified rat CYP2B1 (470%). Western blots showed that microsomes of the two subjects in which CDE metab. was the greatest in the presence of isoflurane were the only samples that had detectable amts. of a 54 kDa protein that was recognized by an antirat CYP2B1; the antibody also selectively recognized expressed **CYP2B6**. The authors conclude that certain halocarbons stimulate CDE metab. in human liver as a function of **CYP2B6**.

ACCESSION NUMBER: 1995:307865 CAPLUS
DOCUMENT NUMBER: 122:74237
TITLE: Isoflurane-chlorodifluoroethene interaction in human liver microsomes: role of cytochrome P4502B6 in potentiation of haloethene metabolism
AUTHOR(S): Baker, Max T.; Olson, Michael J.; Wang, Ying; Ronnenberg, William C., Jr.; Johnson, John T.; Brady, Alexandra N.
CORPORATE SOURCE: Department Anesthesia, University Iowa, Iowa City, IA, 52242-1181, USA
SOURCE: Drug Metab. Dispos. (**1995**), 23(1), 60-4
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Drug Metab. Dispos. (**1995**), 23(1), 60-4
CODEN: DMDSAI; ISSN: 0090-9556
AB Short-chain satd. halocarbons, including isoflurane and the chlorofluorocarbon substitute HCFC-123, can strongly potentiate the cytochrome P 450-dependent oxidn. of gaseous haloethenes, such as 2-chloro-1,1-difluoroethene (CDE) and vinyl chloride, in vivo and in vitro. P 450 isoenzyme specificity in this effect is suggested by the fact that the interaction is pronounced in microsomes from rats treated with phenobarbital, but does not occur in microsomes of isoniazid- or .beta.-naphthoflavone-treated animals. The authors examd. the effect of isoflurane on CDE defluorination in liver microsomes from 10 human organ donors to det. whether satd. halocarbon/haloethene interactions also occur in humans and, if so, to det. the cytochromes P 450 involved. Three of the samples exhibited isoflurane-stimulated increases (24, 32, and 41%) in CDE defluorination; isoflurane either inhibited or had no effect on CDE

metab. in the other seven samples. Two samples in which isoflurane potentiated CDE metab. to the greatest rates had higher **coumarin** 7-hydroxylase (indicative of CYP2A6), 7-ethoxycoumarin O-deethylase (**CYP2B6**), and nifedipine oxidase (CYP3A4) activities than the other eight samples. However, all 10 subjects had similar rates of phenacetin O-deethylation (CYP1A2) and chlorzoxazone 6-hydroxylation (CYP2E1). In microsomes from cells transfected with cDNAs coding for individual human P450s, CDE metab. by **CYP2B6** was stimulated (216%) by isoflurane, whereas isoflurane did not stimulate CDE metab. by human CYP2A6, CYP3A4, CYP2D6, or CYP2E1. Isoflurane highly increased CDE defluorination in purified rat CYP2B1 (470%). Western blots showed that microsomes of the two subjects in which CDE metab. was the greatest in the presence of isoflurane were the only samples that had detectable amts. of a 54 kDa protein that was recognized by an antirat CYP2B1; the antibody also selectively recognized expressed **CYP2B6**. The authors conclude that certain halocarbons stimulate CDE metab. in human liver as a function of **CYP2B6**.

L31 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2002 ACS

AB To study the catalytic activities of human P450s, human P 450 cDNAs were cloned and expressed into active enzymes using cultured cells. By both transient and stable cDNA expression systems, several human P450s were found to be capable of metabolically-activating the human hepatocarcinogen aflatoxin B1. These cDNA expression systems can also be used to det. whether an unknown chem. will be activated by a human P 450 and thus be toxic or mutagenic in humans. To assess the extent of interindividual variation in P 450 expression, probes developed from P 450 cDNAs are being used to quantify levels of P 450 mRNAs in various human tissues. Studies using RNase protection revealed that the closely related **CYP2B6** and CYP2B7 mRNAs could be independently quantified in liver and lung, resp. This procedure can be used to examine expression of different P 450 genes in banks of human tissue specimens.

ACCESSION NUMBER: 1993:553752 CAPLUS
DOCUMENT NUMBER: 119:153752
TITLE: Analysis of human cytochrome P450 catalytic activities and expression
AUTHOR(S): Gonzalez, Frank J.; Crespi, Charles L.; Czerwinski, Maceij; Gelboin, Harry V.
CORPORATE SOURCE: Lab. Mol. Carcinog., Natl. Cancer Inst., MD, USA
SOURCE: Tohoku J. Exp. Med. (**1992**), 168(2), 67-72
CODEN: TJEMAO; ISSN: 0040-8727
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Tohoku J. Exp. Med. (**1992**), 168(2), 67-72
CODEN: TJEMAO; ISSN: 0040-8727

AB To study the catalytic activities of human P450s, human P 450 cDNAs were cloned and expressed into active enzymes using cultured cells. By both transient and stable cDNA expression systems, several human P450s were found to be capable of metabolically-activating the human hepatocarcinogen aflatoxin B1. These cDNA expression systems can also be used to det. whether an unknown chem. will be activated by a human P 450 and thus be toxic or mutagenic in humans. To assess the extent of interindividual variation in P 450 expression, probes developed from P 450 cDNAs are being used to quantify levels of P 450 mRNAs in various human tissues. Studies using RNase protection revealed that the closely related **CYP2B6** and CYP2B7 mRNAs could be independently quantified in liver and lung, resp. This procedure can be used to examine expression of different P 450 genes in banks of human tissue specimens.

IT Lymphoblast
(**B**-cell, **aflatoxin** B1 mutagenicity and toxicity in human, cytochrome P 450 in relation to)

L31 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2002 ACS

AB The relative levels of expression of cytochrome P 450 isoenzymes from eight gene families or subfamilies were measured in a panel of twelve human liver samples to det. the individuality in their expression and whether any forms are coregulated. Isoenzymes were identified in most cases on Western blots based on the mobility of authentic recombinant human cytochrome P 450 stds. The levels of the following P 450 proteins correlated with each other: CYP2A6, **CYP2B6**, and a protein from the CYP2C gene subfamily, CYP2E1, and a member of the CYP2A gene subfamily, CYP2C8, CYP3A3/A4, and total cytochrome P 450 content. Also, the levels of two proteins in the CYP4A gene subfamily were highly correlated. These correlations are consistent with the relative regulation of members of these gene families in rats or mice. In addn., the level of expression of specific isoenzymes has also been compared with the rate of metab. of a panel of drugs, carcinogens, and model P 450 substrates. These latter studies demonstrate and confirm that the correlations obtained in this manner represent a powerful approach towards the assignment of the metab. of substrates by specific human P 450 isoenzymes.

ACCESSION NUMBER: 1992:167953 CAPLUS
DOCUMENT NUMBER: 116:167953
TITLE: Relative expression of cytochrome P 450 isoenzymes in human liver and association with the metabolism of drugs and xenobiotics
AUTHOR(S): Forrester, Lesley M.; Henderson, Colin J.; Glancey, Michael J.; Back, David J.; Park, B. Kevin; Ball, Simon E.; Kitteringham, Neil R.; McLaren, Aileen W.; Miles, John S.; et al.
CORPORATE SOURCE: Mol. Pharmacol. Group, Imp. Cancer Res. Fund, Edinburgh, EH8 9XD, UK
SOURCE: Biochem. J. (**1992**), 281(2), 359-68
CODEN: BIJOAK; ISSN: 0306-3275
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Biochem. J. (**1992**), 281(2), 359-68
CODEN: BIJOAK; ISSN: 0306-3275
AB The relative levels of expression of cytochrome P 450 isoenzymes from eight gene families or subfamilies were measured in a panel of twelve human liver samples to det. the individuality in their expression and whether any forms are coregulated. Isoenzymes were identified in most cases on Western blots based on the mobility of authentic recombinant human cytochrome P 450 stds. The levels of the following P 450 proteins correlated with each other: CYP2A6, **CYP2B6**, and a protein from the CYP2C gene subfamily, CYP2E1, and a member of the CYP2A gene subfamily, CYP2C8, CYP3A3/A4, and total cytochrome P 450 content. Also, the levels of two proteins in the CYP4A gene subfamily were highly correlated. These correlations are consistent with the relative regulation of members of these gene families in rats or mice. In addn., the level of expression of specific isoenzymes has also been compared with the rate of metab. of a panel of drugs, carcinogens, and model P 450 substrates. These latter studies demonstrate and confirm that the correlations obtained in this manner represent a powerful approach towards the assignment of the metab. of substrates by specific human P 450 isoenzymes.

IT 9015-81-0 9038-14-6, Monooxygenase 9039-06-9, Cytochrome P450 reductase 9075-83-6 39401-02-0, **Coumarin** 7-hydroxylase 42613-26-3, Ethoxycoumarin O-de-ethylase 59793-97-4, Ethoxyresorufin O-de-ethylase 70431-16-2, Estradiol 2-hydroxylase 72750-64-2, Methoxycoumarin O-demethylase 84067-29-8, Diazepam N-demethylase 84067-35-6, Diazepam 3-hydroxylase 106527-94-0, Tolbutamide hydroxylase 111693-78-8 123303-24-2 127737-48-8 139946-22-8 139946-24-0 139946-25-1 139946-26-2 139946-28-4 139946-44-4 139946-45-5 139946-46-6 139946-47-7
RL: BIOL (Biological study)
(of human liver, cytochrome P 450 isoforms expression and drug and xenobiotic metab. in relation to)

=>

=> d l7 abs ibib kwic 1-4

L7 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS

AB **CYP2A6** is the principle enzyme metabolizing **nicotine** to its inactive metabolite **cotinine**. In this study, the selective probe reactions for each major cytochrome P 450 were used to evaluate the specificity and selectivity of the **CYP2A6** inhibitors **methoxsalen**, tranylcypromine, and tryptamine in cDNA-expressing and human liver microsomes. Phenacetin O-deethylation (CYP1A2), coumarin 7-hydroxylation (**CYP2A6**), diclofenac 4'-hydroxylation (CYP2C9), omeprazole 5-hydroxylation (CYP2C19), dextromethorphan O-demethylation (CYP2D6), 7-ethoxy-4-trifluoromethylcoumarin deethylation (**CYP2B6**), p-nitrophenol hydroxylation (CYP2E1), and omeprazole sulfonation (CYP3A4) were used as index reactions. Apparent Ki values for inhibition of P450s' (1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4) activities showed that tranylcypromine, **methoxsalen**, and tryptamine have high specificity and relative selectivity for **CYP2A6**. In cDNA-expressing microsomes, tranylcypromine inhibited **CYP2A6** (Ki = 0.08 .mu.M) with about 60- to 5000-fold greater potency relative to other P450s. **Methoxsalen** inhibited **CYP2A6** (Ki = 0.8 .mu.M) with about 3.5- 94-fold greater potency than other P450s, except for CYP1A2 (Ki = 0.2 .mu.M). Tryptamine inhibited **CYP2A6** (Ki = 1.7 .mu.M) with about 6.5- 213-fold greater potency relative to other P450s, except for CYP1A2 (Ki = 1.7 .mu.M). Similar results were also obtained with **methoxsalen** and tranylcypromine in human liver microsomes. R-(+)-Tranylcypromine, (.+-.)-tranylcypromine, and S-(-)-tranylcypromine competitively inhibited **CYP2A6**-mediated metab. of **nicotine** with apparent Ki values of 0.05, 0.08, and 2.0 .mu.M, resp. Tranylcypromine [particularly R-(+) isomer], tryptamine, and **methoxsalen** are specific and relatively selective for **CYP2A6** and may be useful in vivo to decrease **smoking** by inhibiting **nicotine** metab. with a low risk of metabolic drug interactions.

ACCESSION NUMBER: 2001:392449 CAPLUS
DOCUMENT NUMBER: 135:146768
TITLE: Evaluation of **methoxsalen**, tranylcypromine, and tryptamine as specific and selective **CYP2A6** inhibitors in vitro
AUTHOR(S): Zhang, Wenjiang; Kilicarslan, Tansel; Tyndale, Rachel F.; Sellers, Edward M.
CORPORATE SOURCE: Department of Pharmacology, University of Toronto, Toronto, ON, Can.
SOURCE: Drug Metabolism and Disposition (2001), 29(6), 897-902
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Evaluation of **methoxsalen**, tranylcypromine, and tryptamine as specific and selective **CYP2A6** inhibitors in vitro

AB **CYP2A6** is the principle enzyme metabolizing **nicotine** to its inactive metabolite **cotinine**. In this study, the selective probe reactions for each major cytochrome P 450 were used to evaluate the specificity and selectivity of the **CYP2A6**

inhibitors **methoxsalen**, tranylcypromine, and tryptamine in cDNA-expressing and human liver microsomes. Phenacetin O-deethylation (CYP1A2), coumarin 7-hydroxylation (**CYP2A6**), diclofenac 4'-hydroxylation (CYP2C9), omeprazole 5-hydroxylation (CYP2C19), dextromethorphan O-demethylation (CYP2D6), 7-ethoxy-4-trifluoromethylcoumarin deethylation (**CYP2B6**), p-nitrophenol hydroxylation (CYP2E1), and omeprazole sulfonation (CYP3A4) were used as index reactions. Apparent Ki values for inhibition of P450s' (1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4) activities showed that tranylcypromine, **methoxsalen**, and tryptamine have high specificity and relative selectivity for **CYP2A6**. In cDNA-expressing microsomes, tranylcypromine inhibited **CYP2A6** (Ki = 0.08 .mu.M) with about 60- to 5000-fold greater potency relative to other P450s. **Methoxsalen** inhibited **CYP2A6** (Ki = 0.8 .mu.M) with about 3.5- 94-fold greater potency than other P450s, except for CYP1A2 (Ki = 0.2 .mu.M). Tryptamine inhibited **CYP2A6** (Ki = 1.7 .mu.M) with about 6.5- 213-fold greater potency relative to other P450s, except for CYP1A2 (Ki = 1.7 .mu.M). Similar results were also obtained with **methoxsalen** and tranylcypromine in human liver microsomes. R-(+)-Tranylcypromine, (.+-.)-tranylcypromine, and S-(-)-tranylcypromine competitively inhibited **CYP2A6**-mediated metab. of **nicotine** with apparent Ki values of 0.05, 0.08, and 2.0 .mu.M, resp. Tranylcypromine [particularly R-(+) isomer], tryptamine, and **methoxsalen** are specific and relatively selective for **CYP2A6** and may be useful in vivo to decrease **smoking** by inhibiting **nicotine** metab. with a low risk of metabolic drug interactions.

ST cytochrome P4502A6 inhibitor **methoxsalen** tranylcypromine tryptamine **nicotine** metab; **smoking nicotine** dependence metab cytochrome P4502A6 tranylcypromine

IT Enzyme kinetics
(of inhibition; evaluation of **methoxsalen**, tranylcypromine, and tryptamine as specific and selective **CYP2A6** inhibitors in vitro)

IT 61-54-1, Tryptamine 155-09-9, Tranylcypromine **298-81-7**, **Methoxsalen** 3721-26-4, (-)-Tranylcypromine 3721-28-6, (+)-Tranylcypromine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(evaluation of **methoxsalen**, tranylcypromine, and tryptamine as specific and selective **CYP2A6** inhibitors in vitro)

IT 54-11-5, **Nicotine** 329736-03-0, cytochrome P 450 3A4 329978-01-0, cytochrome P 450 2C9 330196-64-0, cytochrome P 450 1A2 330196-93-5, cytochrome P 450 2E1 330207-11-9, cytochrome P 450 2B6 330589-90-7, cytochrome P 450 2C19 330597-62-1, cytochrome P 450 2D6 331827-06-6, cytochrome P450 2A6
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(evaluation of **methoxsalen**, tranylcypromine, and tryptamine as specific and selective **CYP2A6** inhibitors in vitro)

IT 486-56-6, **Cotinine**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(evaluation of **methoxsalen**, tranylcypromine, and tryptamine as specific and selective **CYP2A6** inhibitors in vitro)

L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS

AB N-Nitrosobenzylmethylamine (NBzMA) is a potent esophageal carcinogen in

rodents, and has been found as a dietary contaminant in certain areas of China where esophageal cancer is endemic. To det. which cytochrome P 450 enzymes in humans are primarily responsible for NBzMA metab., microsomes from lymphoblastoid cell lines expressing a panel of human cytochrome P-450s (CYP1A1, CYP1A2, **CYP2A6**, **CYP2B6**, CYP2D6, CYP2E1, CYP2C9, CYP2C19, and CYP3A4) and a panel of 10 different human liver microsomal prepns. were examd. for their abilities to metabolize [3H]NBzMA. In addn., the ability of human liver microsomes to form various NBzMA metabolites was correlated with the abilities of these prepns. to metabolize coumarin, ethoxyresorufin, chlorzoxazone, 7-ethoxy-4-trifluoromethylcoumarin, S-mephenytoin, and nifedipine. NBzMA metabolites were quantitated by reversed-phase high-performance liq. chromatog. (HPLC) coupled with flow-through radioactivity detection. Major metabolites included benzaldehyde, benzyl alc., benzoic acid, and several uncharacterized radioactive peaks. Of the representative P 450 activities, only CYP2E1 and **CYP2A6** catalyzed substantial metab. of NBzMA. Compared to CYP2E1, **CYP2A6** metabolized NBzMA more readily. NBzMA acted as a potent inhibitor of coumarin 7-hydroxylation in **CYP2A6** microsomes. Human liver microsomes metabolized NBzMA readily. NBzMA metabolite formation was most highly correlated with coumarin 7-hydroxylase activity, a marker of **CYP2A6** activity. 8-Methoxypsoralen substantially inhibited NBzMA metab. in human hepatic microsomes. When the effects of the potent isothiocyanates PEITC and PHITC were analyzed on microsomes from cell lines expressing CYP2E1 and **CYP2A6**, it was found that PEITC inhibited both enzymes, PHITC was the more effective inhibitor of CYP2E1, and PHITC was an ineffective inhibitor of **CYP2A6**. Collectively, these data indicate that **CYP2A6** and, to a lesser degree, CYP2E1 are important P 450 enzymes in the activation of NBzMA in human systems.

ACCESSION NUMBER: 1999:779961 CAPLUS
DOCUMENT NUMBER: 132:103991
TITLE: Metabolism of N-nitrosobenzylmethylamine by human cytochrome P-450 enzymes
AUTHOR(S): Morse, Mark A.; Lu, Jerry; Stoner, Gary D.; Murphy, Sharon E.; Peterson, Lisa A.
CORPORATE SOURCE: Division of Environmental Health Sciences, Ohio State University School of Public Health, Columbus, OH, USA
SOURCE: Journal of Toxicology and Environmental Health, Part A (1999), 58(7), 397-411
CODEN: JTEHF8
PUBLISHER: Taylor & Francis
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB N-Nitrosobenzylmethylamine (NBzMA) is a potent esophageal carcinogen in rodents, and has been found as a dietary contaminant in certain areas of China where esophageal cancer is endemic. To det. which cytochrome P 450 enzymes in humans are primarily responsible for NBzMA metab., microsomes from lymphoblastoid cell lines expressing a panel of human cytochrome P-450s (CYP1A1, CYP1A2, **CYP2A6**, **CYP2B6**, CYP2D6, CYP2E1, CYP2C9, CYP2C19, and CYP3A4) and a panel of 10 different human liver microsomal prepns. were examd. for their abilities to metabolize [3H]NBzMA. In addn., the ability of human liver microsomes to form various NBzMA metabolites was correlated with the abilities of these prepns. to metabolize coumarin, ethoxyresorufin, chlorzoxazone, 7-ethoxy-4-trifluoromethylcoumarin, S-mephenytoin, and nifedipine. NBzMA metabolites were quantitated by reversed-phase high-performance liq.

chromatog. (HPLC) coupled with flow-through radioactivity detection. Major metabolites included benzaldehyde, benzyl alc., benzoic acid, and several uncharacterized radioactive peaks. Of the representative P 450 activities, only CYP2E1 and **CYP2A6** catalyzed substantial metab. of NBzMA. Compared to CYP2E1, **CYP2A6** metabolized NBzMA more readily. NBzMA acted as a potent inhibitor of coumarin 7-hydroxylation in **CYP2A6** microsomes. Human liver microsomes metabolized NBzMA readily. NBzMA metabolite formation was most highly correlated with coumarin 7-hydroxylase activity, a marker of **CYP2A6** activity. 8-Methoxypsoralen substantially inhibited NBzMA metab. in human hepatic microsomes. When the effects of the potent isothiocyanates PEITC and PHITC were analyzed on microsomes from cell lines expressing CYP2E1 and **CYP2A6**, it was found that PEITC inhibited both enzymes, PHITC was the more effective inhibitor of CYP2E1, and PHITC was an ineffective inhibitor of **CYP2A6**. Collectively, these data indicate that **CYP2A6** and, to a lesser degree, CYP2E1 are important P 450 enzymes in the activation of NBzMA in human systems.

IT **298-81-7**, 8-Methoxypsoralen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effects on formation of benzyl alc. and benzoate from nitrosobenzylmethylamine; N-nitrosobenzylmethylamine metab. by human cytochrome P 450 enzymes)

L7 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS

AB Comparison of 7-hydroxylation of coumarin, a **CYP2A6** substrate, in human and African green and cynomolgus monkey liver microsomes was made by an HPLC assay with UV detection. In human liver microsomes, the Km and Vmax values for the metabolic conversion were 2.1 .mu.M and 0.79 nmol/mg/min, resp. While African green monkey showed Km and Vmax values of 2.7 .mu.M and 0.52 nmol/mg/min, which were similar to human, higher Km and Vmax values were found in cynomolgus monkey. Coumarin 7-hydroxylation in human and African green monkey was selectively inhibited by **methoxsalen** and pilocarpine (**CYP2A6** inhibitors) but not by other inhibitors, i.e. .alpha.-naphthoflavone (CYP1A1), orphenadrine (**CYP2B6**), sulfaphenazole (CYP2C9), quinidine (CYP2D6), and ketoconazole (CYP3A4). Immunoinhibition results supported **CYP2A6** involvement in human and its homolog in monkey in coumarin 7-hydroxylation, as only anti-**CYP2A6**, but not CYP2B1, CYP2C13, CYP2D6, CYP2E1, or CYP3A antibodies, inhibited this conversion. African green monkey was similar to human in catalytic activity of coumarin 7-hydroxylation and response to **CYP2A6** inhibitors or antibody inhibition. However, the monkey **CYP2A6** is not identical to the human in that Ki values were different, and differences were obsd. with some **CYP2A6** inhibitors, such as **nicotine** and **methoxsalen**, suggesting that, under some circumstances, studies of **nicotine** kinetics and drug taking behavior in monkey may not be comparable to human.

ACCESSION NUMBER: 1998:150136 CAPLUS
DOCUMENT NUMBER: 128:164257
TITLE: Comparison of **CYP2A6** catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes
AUTHOR(S): Li, Yan; Li, Ning Yuan; Sellers, Edward M.
CORPORATE SOURCE: Dep. Pharmacology, Medicine, Psychiatry, Univ. Toronto, Toronto, ON, M5S 1A8, Can.
SOURCE: Eur. J. Drug Metab. Pharmacokinet. (1997), 22(4), 295-304
CODEN: EJDPD2; ISSN: 0378-7966

PUBLISHER: Medecine et Hygiene
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Comparison of **CYP2A6** catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes

AB Comparison of 7-hydroxylation of coumarin, a **CYP2A6** substrate, in human and African green and cynomolgus monkey liver microsomes was made by an HPLC assay with UV detection. In human liver microsomes, the Km and Vmax values for the metabolic conversion were 2.1 .mu.M and 0.79 nmol/mg/min, resp. While African green monkey showed Km and Vmax values of 2.7 .mu.M and 0.52 nmol/mg/min, which were similar to human, higher Km and Vmax values were found in cynomolgus monkey. Coumarin 7-hydroxylation in human and African green monkey was selectively inhibited by **methoxsalen** and pilocarpine (**CYP2A6** inhibitors) but not by other inhibitors, i.e. .alpha.-naphthoflavone (CYP1A1), orphenadrine (**CYP2B6**), sulfaphenazole (CYP2C9), quinidine (CYP2D6), and ketoconazole (CYP3A4). Immunoinhibition results supported **CYP2A6** involvement in human and its homolog in monkey in coumarin 7-hydroxylation, as only anti-**CYP2A6**, but not CYP2B1, CYP2C13, CYP2D6, CYP2E1, or CYP3A antibodies, inhibited this conversion. African green monkey was similar to human in catalytic activity of coumarin 7-hydroxylation and response to **CYP2A6** inhibitors or antibody inhibition. However, the monkey **CYP2A6** is not identical to the human in that Ki values were different, and differences were obsd. with some **CYP2A6** inhibitors, such as **nicotine** and **methoxsalen**, suggesting that, under some circumstances, studies of **nicotine** kinetics and drug taking behavior in monkey may not be comparable to human.

IT Enzyme kinetics
Michaelis constant
Microsome
Monkey
(comparison of **CYP2A6** catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes)

IT Monoclonal antibodies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(selective inhibition of coumarin 7-hydroxylation by **CYP2A6** monoclonal antibody)

IT 9035-51-2, Cytochrome P 450, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**CYP2A6**; comparison of **CYP2A6** catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes)

IT 93-35-6, 7-Hydroxycoumarin
RL: BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(comparison of **CYP2A6** catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes)

IT 91-64-5, Coumarin
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(comparison of **CYP2A6** catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes)

IT 92-13-7, Pilocarpine **298-81-7, Methoxsalen**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(selective inhibition of coumarin 7-hydroxylation by)

L7 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2002 ACS

AB We evaluated the specificity of 15 substrates and 14 inhibitors of the cytochrome P450s using nine human P 450 isoforms expressed in HepG2 cells using a recombinant vaccinia virus and also in human liver microsomes. Coumarin, 7-ethoxyresorufin, 7-benzyloxyresorufin, tolbutamide, aniline and diazepam were isoform-selective substrates towards **CYP2A6**, the CYP1A subfamily, **CYP2B6**, the CYP2C subfamily, CYP2E1 and the CYP3A subfamily, resp. However, a selective substrate for CYP2D6 was not found among the chems. tested. SKF-525A inhibited > 40% of the metabolic activity of all substrates tested, and the inhibitory effects differed among P 450 isoforms. Sulfaphenazole, 7,8-benzoflavone, quinidine and troleandomycin were selective inhibitors of the CYP2C subfamily (except CYP2C19), the CYP1A subfamily, CYP2D6 and the CYP3A subfamily, resp. **Methoxsalen** (**CYP2A6** inhibitor) inhibited the metabolic activity of CYP1A2 as well as that of **CYP2A6**. Diethyldithiocarbamate (CYP2E1 inhibitor) inhibited the metabolic activities of **CYP2A6** and CYP2C19 in addn. to that of CYP2E1. Our results indicated that substrates and inhibitors reported as P 450 selective probes are not necessarily specific for individual human P 450 isoforms. These results may provide useful information regarding human P 450 substrates and inhibitors in vitro using human liver microsomal samples.

ACCESSION NUMBER:	1996:424712 CAPLUS
DOCUMENT NUMBER:	125:80284
TITLE:	Specificity of substrate and inhibitor probes for cytochrome P450s: evaluation of in vitro metabolism using cDNA-expressed human P450s and human liver microsomes
AUTHOR(S):	Ono, S.; Hatanaka, T.; Hotta, H.; Satoh, T.; Gonzalez, F. J.; Tsutsui, M.
CORPORATE SOURCE:	Amersham K.K., Central Lab. for Research and Development, Chiba, 270-14, Japan
SOURCE:	Xenobiotica (1996), 26(7), 681-693 CODEN: XENOBH; ISSN: 0049-8254
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB We evaluated the specificity of 15 substrates and 14 inhibitors of the cytochrome P450s using nine human P 450 isoforms expressed in HepG2 cells using a recombinant vaccinia virus and also in human liver microsomes. Coumarin, 7-ethoxyresorufin, 7-benzyloxyresorufin, tolbutamide, aniline and diazepam were isoform-selective substrates towards **CYP2A6**, the CYP1A subfamily, **CYP2B6**, the CYP2C subfamily, CYP2E1 and the CYP3A subfamily, resp. However, a selective substrate for CYP2D6 was not found among the chems. tested. SKF-525A inhibited > 40% of the metabolic activity of all substrates tested, and the inhibitory effects differed among P 450 isoforms. Sulfaphenazole, 7,8-benzoflavone, quinidine and troleandomycin were selective inhibitors of the CYP2C subfamily (except CYP2C19), the CYP1A subfamily, CYP2D6 and the CYP3A subfamily, resp. **Methoxsalen** (**CYP2A6** inhibitor) inhibited the metabolic activity of CYP1A2 as well as that of **CYP2A6**. Diethyldithiocarbamate (CYP2E1 inhibitor) inhibited the metabolic activities of **CYP2A6** and CYP2C19 in addn. to that of CYP2E1. Our results indicated that substrates and inhibitors reported as P 450 selective probes are not necessarily specific for individual human P 450 isoforms. These results may provide useful information regarding human P 450 substrates and inhibitors in vitro using human liver microsomal samples.

IT 51-03-6, Piperonyl butoxide 56-54-2, Quinidine 62-68-0, SKF-525A

117-39-5, Quercetin 147-84-2, biological studies 155-09-9, Tranylcypromine **298-81-7**, **Methoxsalen** 519-23-3, Ellipticine 526-08-9, Sulfaphenazole 604-59-1, 7,8-Benzoflavone 2751-09-9, Troleandomycin 7554-65-6, 4-Methylpyrazole 65277-42-1, Ketoconazole 80288-49-9, Furafylline
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(specificity of substrate and inhibitor probes for cytochrome P 450 isoforms)

=> s l4 and py<=1997
L22 19 L4 AND PY<=1997

=> d l22 abs ibib kwic 1-19

L22 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2002 ACS
AB Comparison of 7-hydroxylation of coumarin, a **CYP2A6** substrate, in human and African green and cynomolgus monkey liver microsomes was made by an HPLC assay with UV detection. In human liver microsomes, the Km and Vmax values for the metabolic conversion were 2.1 .mu.M and 0.79 nmol/mg/min, resp. While African green monkey showed Km and Vmax values of 2.7 .mu.M and 0.52 nmol/mg/min, which were similar to human, higher Km and Vmax values were found in cynomolgus monkey. Coumarin 7-hydroxylation in human and African green monkey was selectively inhibited by **methoxsalen** and pilocarpine (**CYP2A6** inhibitors) but not by other inhibitors, i.e. .alpha.-naphthoflavone (CYP1A1), orphenadrine (CYP2B6), sulfaphenazole (CYP2C9), quinidine (CYP2D6), and ketoconazole (CYP3A4). Immunoinhibition results supported **CYP2A6** involvement in human and its homolog in monkey in coumarin 7-hydroxylation, as only anti-**CYP2A6**, but not CYP2B1, CYP2C13, CYP2D6, CYP2E1, or CYP3A antibodies, inhibited this conversion. African green monkey was similar to human in catalytic activity of coumarin 7-hydroxylation and response to **CYP2A6** inhibitors or antibody inhibition. However, the monkey **CYP2A6** is not identical to the human in that Ki values were different, and differences were obsd. with some **CYP2A6** inhibitors, such as **nicotine** and **methoxsalen**, suggesting that, under some circumstances, studies of **nicotine** kinetics and drug taking behavior in monkey may not be comparable to human.

ACCESSION NUMBER: 1998:150136 CAPLUS
DOCUMENT NUMBER: 128:164257
TITLE: Comparison of **CYP2A6** catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes
AUTHOR(S): Li, Yan; Li, Ning Yuan; Sellers, Edward M.
CORPORATE SOURCE: Dep. Pharmacology, Medicine, Psychiatry, Univ. Toronto, Toronto, ON, M5S 1A8, Can.
SOURCE: Eur. J. Drug Metab. Pharmacokinet. (**1997**), 22(4), 295-304
CODEN: EJDPD2; ISSN: 0378-7966
PUBLISHER: Medecine et Hygiene
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Comparison of **CYP2A6** catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes
SO Eur. J. Drug Metab. Pharmacokinet. (**1997**), 22(4), 295-304
CODEN: EJDPD2; ISSN: 0378-7966
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(CYP3A4). Immunoinhibition results supported **CYP2A6** involvement in human and its homolog in monkey in coumarin 7-hydroxylation, as only anti-**CYP2A6**, but not CYP2B1, CYP2C13, CYP2D6, CYP2E1, or CYP3A antibodies, inhibited this conversion. African green monkey was similar to human in catalytic activity of coumarin 7-hydroxylation and response to **CYP2A6** inhibitors or antibody inhibition. However, the monkey **CYP2A6** is not identical to the human in that Ki values were different, and differences were obsd. with some **CYP2A6** inhibitors, such as **nicotine** and **methoxsalen**, suggesting that, under some circumstances, studies of **nicotine** kinetics and drug taking behavior in monkey may not be comparable to human.

IT Enzyme kinetics
Michaelis constant
Microsome
Monkey
(comparison of **CYP2A6** catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes)

IT Monoclonal antibodies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(selective inhibition of coumarin 7-hydroxylation by **CYP2A6** monoclonal antibody)

IT 9035-51-2, Cytochrome P 450, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**CYP2A6**; comparison of **CYP2A6** catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes)

IT 93-35-6, 7-Hydroxycoumarin
RL: BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(comparison of **CYP2A6** catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes)

IT 91-64-5, Coumarin
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(comparison of **CYP2A6** catalytic on coumarin 7-hydroxylation in human and monkey liver microsomes)

IT 92-13-7, Pilocarpine **298-81-7**, **Methoxsalen**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(selective inhibition of coumarin 7-hydroxylation by)

L22 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB Nine org. solvents and 47 commonly used P 450 substrates and inhibitors were examd. for their effects on coumarin 7-hydroxylase (**CYP2A6**) activity in human liver microsomes. Of the nine org. solvents examd. (final concn. 1%, vol./vol.), only methanol did not inhibit the 7-hydroxylation of coumarin (0.5 to 50 .mu.M) by human liver microsomes. Dioxane and THF, which are structurally related to coumarin, were the most inhibitory solvents examd. Although the rates of coumarin 7-hydroxylation varied enormously among nine samples of human liver microsomes and cDNA-expressed **CYP2A6** (Vmax = 179 to 2470 pmol/mg protein/min), the Km for coumarin 7-hydroxylation was fairly const. (ranging from 0.50 to 0.70 .mu.M). The following chems. caused little or no inhibition of **CYP2A6** as defined by a Ki > 200 .mu.M: caffeine, chlorzoxazone, cimetidine, dextromethorphan, diazepam, diclofenac, erythromycin, ethynylestradiol, ethynyltestosterone, fluconazole, furafylline, furfural, hexobarbital, itraconazole, mephenytoin, methimazole, metronidazole,

naringenin, naringin, nifedipine, norfloxacin, norgestrel, orphenadrine, quinidine, papaverine, phenacetin, pyrimethamine, ranitidine, spironolactone, sulfaphenazole, sulfinpyrazone, testosterone, tolbutamide, troleandomycin, and warfarin. In other words, these chems., at a final concn. of 100 .mu.M, failed to inhibit **CYP2A6** when the concn. of coumarin was equal to Km (0.50 .mu.M). The following chems. were classified as strong inhibitors of **CYP2A6** (defined by Ki < 200 .mu.M): clotrimazole, diethyldithiocarbamate, ellipticine, ketoconazole, 8-methoxypsoralen, 4-methylpyrazole, metyrapone, miconazole, .alpha.-naphthoflavone, **nicotine**, p-nitrophenol, and tranylcypromine. The potency with which each chem. inhibited the 7-hydroxylation of coumarin was independent of which sample of human liver microsomes was studied. One of the most potent inhibitors of coumarin 7-hydroxylase was 8-methoxypsoralen (**methoxsalen**), which was detd. to be a mechanism-based inhibitor (suicide substrate) of **CYP2A6** (kinactivation 0.5 min-1). With the exception of 8-methoxypsoralen, preincubation of human liver microsomes and NADPH with the aforementioned inhibitors did not increase their ability to inhibit **CYP2A6**. The most potent competitive inhibitor of **CYP2A6** was tranylcypromine (Ki = 0.04 .mu.M). Several of the chems. that strongly inhibited **CYP2A6**, such as ketoconazole and tranylcypromine, are often used with the intention of selectively inhibiting human P 450 enzymes other than **CYP2A6**.

ACCESSION NUMBER: 1997:287113 CAPLUS
DOCUMENT NUMBER: 126:273360
TITLE: Inhibition of coumarin 7-hydroxylase activity in human liver microsomes
AUTHOR(S): Draper, Alison J.; Madan, Ajay; Parkinson, Andrew
CORPORATE SOURCE: Dep. Pharmacol., Toxicol., Therapeutics, Cent. Environ. Occupational Health, Univ. Kansas Med. Cent., Kansas City, KS, 66160-7417, USA
SOURCE: Arch. Biochem. Biophys. (**1997**), 341(1), 47-61
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Arch. Biochem. Biophys. (**1997**), 341(1), 47-61
CODEN: ABBIA4; ISSN: 0003-9861

AB Nine org. solvents and 47 commonly used P 450 substrates and inhibitors were examd. for their effects on coumarin 7-hydroxylase (**CYP2A6**) activity in human liver microsomes. Of the nine org. solvents examd. (final concn. 1%, vol./vol.), only methanol did not inhibit the 7-hydroxylation of coumarin (0.5 to 50 .mu.M) by human liver microsomes. Dioxane and THF, which are structurally related to coumarin, were the most inhibitory solvents examd. Although the rates of coumarin 7-hydroxylation varied enormously among nine samples of human liver microsomes and cDNA-expressed **CYP2A6** (Vmax = 179 to 2470 pmol/mg protein/min), the Km for coumarin 7-hydroxylation was fairly const. (ranging from 0.50 to 0.70 .mu.M). The following chems. caused little or no inhibition of **CYP2A6** as defined by a Ki > 200 .mu.M: caffeine, chlorzoxazone, cimetidine, dextromethorphan, diazepam, diclofenac, erythromycin, ethynylestradiol, ethynyltestosterone, fluconazole, furafylline, furfural, hexobarbital, itraconazole, mephenytoin, methimazole, metronidazole, naringenin, naringin, nifedipine, norfloxacin, norgestrel, orphenadrine, quinidine, papaverine, phenacetin, pyrimethamine, ranitidine, spironolactone, sulfaphenazole, sulfinpyrazone, testosterone, tolbutamide, troleandomycin, and warfarin. In other words, these chems., at a final

concn. of 100 .mu.M, failed to inhibit **CYP2A6** when the concn. of coumarin was equal to Km (0.50 .mu.M). The following chems. were classified as strong inhibitors of **CYP2A6** (defined by Ki < 200 .mu.M): clotrimazole, diethyldithiocarbamate, ellipticine, ketoconazole, 8-methoxypsoralen, 4-methylpyrazole, metyrapone, miconazole, .alpha.-naphthoflavone, **nicotine**, p-nitrophenol, and tranylcypromine. The potency with which each chem. inhibited the 7-hydroxylation of coumarin was independent of which sample of human liver microsomes was studied. One of the most potent inhibitors of coumarin 7-hydroxylase was 8-methoxypsoralen (**methoxsalen**), which was detd. to be a mechanism-based inhibitor (suicide substrate) of **CYP2A6** (kinactivation 0.5 min-1). With the exception of 8-methoxypsoralen, preincubation of human liver microsomes and NADPH with the aforementioned inhibitors did not increase their ability to inhibit **CYP2A6**. The most potent competitive inhibitor of **CYP2A6** was tranylcypromine (Ki = 0.04 .mu.M). Several of the chems. that strongly inhibited **CYP2A6**, such as ketoconazole and tranylcypromine, are often used with the intention of selectively inhibiting human P 450 enzymes other than **CYP2A6**.

IT 50-12-4, Mephenytoin 52-01-7, Spironolactone 54-11-5, **Nicotine** 54-36-4, Metyrapone 56-29-1, Hexobarbital 56-54-2, Quinidine 57-63-6, Ethynylestradiol 57-96-5, Sulfinpyrazone 58-08-2, Caffeine, biological studies 58-14-0, Pyrimethamine 58-22-0, Testosterone 58-74-2, Papaverine 60-56-0, Methimazole 62-44-2, Phenacetin 64-17-5, Ethanol, biological studies 64-77-7, Tolbutamide 67-56-1, Methanol, biological studies 67-63-0, 2-Propanol, biological studies 67-64-1, Acetone, biological studies 67-68-5, DMSO, biological studies 68-12-2, DMF, biological studies 75-05-8, Acetonitrile, biological studies 81-81-2, Warfarin 83-98-7, Orphenadrine 95-25-0, Chlorzoxazone 98-01-1, Furfural, biological studies 100-02-7, p-Nitrophenol, biological studies 109-99-9, Tetrahydrofuran, biological studies 114-07-8, Erythromycin 123-91-1, Dioxane, biological studies 125-71-3, Dextromethorphan 147-84-2, biological studies 155-09-9, Tranylcypromine **298-81-7**, 8-Methoxypsoralen 434-03-7 439-14-5, Diazepam 443-48-1, Metronidazole 480-41-1, Naringenin 519-23-3, Ellipticine 526-08-9, Sulfaphenazole 604-59-1, .alpha.-Naphthoflavone 2751-09-9, Troleandomycin 6533-00-2, Norgestrel 7554-65-6, 4-Methylpyrazole 10236-47-2, Naringin 15307-86-5, Diclofenac 21829-25-4, Nifedipine 22916-47-8, Miconazole 23593-75-1, Clotrimazole 51481-61-9, Cimetidine 65277-42-1, Ketoconazole 66357-35-5, Ranitidine 70458-96-7, Norfloxacin 80288-49-9, Furafylline 84625-61-6, Itraconazole 86386-73-4, Fluconazole
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(coumarin hydroxylase inhibition in human liver microsomes)

L22 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB Cytochrome P 450 2A3 (CYP2A3) was previously identified in rat lung by cDNA cloning and recently found to be expressed at a high level in the olfactory mucosa. In the current study, CYP2A3 was expressed in insect cells lacking endogenous cytochrome P 450 (P 450) activity, and the substrate specificity of the recombinant cytochrome was characterized and compared with that of **CYP2A6**, a human ortholog of rat CYP2A3, which has been detected in human olfactory mucosa as well as in liver. The CYP2A3 and **CYP2A6** cDNAs were cloned into baculovirus, and recombinant viruses were used to produce active enzymes in Spodoptera frugiperta (SF9) cells. The metabolic activities of S. frugiperta cell microsomal fractions contg. CYP2A3 or **CYP2A6** were studied in a reconstituted system with purified rabbit NADPH-P 450 reductase. CYP2A3

was active toward testosterone, producing 15.alpha.-hydroxytestosterone and several other metabolites, but it had only low activity toward coumarin. **CYP2A6** was active toward coumarin but not toward testosterone. However, both enzymes were active in the metabolic activation of hexamethylphosphoramide, a nasal procarcinogen, and 2,6-dichlorobenzonitrile (DCBN), a herbicide known to cause tissue-specific toxicity in the olfactory mucosa of rodents at very low doses. In addn., both enzymes were active toward 4-nitrophenol, a preferred substrate for CYP2E1. Consistent with CYP2A3 being a major catalyst in microsomal metab. of DCBN, the activities of both CYP2A3 and rat olfactory microsomes in DCBN metab. were inhibited strongly by metyrapone and **methoxsalen** (ID50 <1 .mu.M, with DCBN at 30 .mu.M), but only marginally by 4-methylpyrazole, an inhibitor of CYP2E1. In contrast, the activity of **CYP2A6** was only weakly inhibited by metyrapone or **methoxsalen** (ID50 >50 .mu.M). Thus, rat CYP2A3 and human **CYP2A6** have differences in substrate specificity as well as tissue distribution. These findings should be taken into account when assessing the risk of exposure to potential nasal toxicants in humans.

ACCESSION NUMBER: 1996:655372 CAPLUS
DOCUMENT NUMBER: 125:295026
TITLE: Baculovirus-mediated expression and characterization of rat CYP2A3 and human **CYP2A6**: role in metabolic activation of nasal toxicants
AUTHOR(S): Liu, Cheng; Zhuo, Xiaoliang; Gonzalez, Frank J.; Ding, Xinxin
CORPORATE SOURCE: Laboratory Human Toxicology and Molecular Epidemiology, State University New York, Albany, NY, 12201-0509, USA
SOURCE: Mol. Pharmacol. (**1996**), 50(4), 781-788
CODEN: MOPMA3; ISSN: 0026-895X
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Baculovirus-mediated expression and characterization of rat CYP2A3 and human **CYP2A6**: role in metabolic activation of nasal toxicants

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CODEN: MOPMA3; ISSN: 0026-895X

AB Cytochrome P 450 2A3 (CYP2A3) was previously identified in rat lung by cDNA cloning and recently found to be expressed at a high level in the olfactory mucosa. In the current study, CYP2A3 was expressed in insect cells lacking endogenous cytochrome P 450 (P 450) activity, and the substrate specificity of the recombinant cytochrome was characterized and compared with that of **CYP2A6**, a human ortholog of rat CYP2A3, which has been detected in human olfactory mucosa as well as in liver. The CYP2A3 and **CYP2A6** cDNAs were cloned into baculovirus, and recombinant viruses were used to produce active enzymes in Spodoptera frugiperta (SF9) cells. The metabolic activities of S. frugiperta cell microsomal fractions contg. CYP2A3 or **CYP2A6** were studied in a reconstituted system with purified rabbit NADPH-P 450 reductase. CYP2A3 was active toward testosterone, producing 15.alpha.-hydroxytestosterone and several other metabolites, but it had only low activity toward coumarin. **CYP2A6** was active toward coumarin but not toward testosterone. However, both enzymes were active in the metabolic activation of hexamethylphosphoramide, a nasal procarcinogen, and 2,6-dichlorobenzonitrile (DCBN), a herbicide known to cause tissue-specific toxicity in the olfactory mucosa of rodents at very low doses. In addn., both enzymes were active toward 4-nitrophenol, a preferred substrate for CYP2E1. Consistent with CYP2A3 being a major

catalyst in microsomal metab. of DCBN, the activities of both CYP2A3 and rat olfactory microsomes in DCBN metab. were inhibited strongly by metyrapone and **methoxsalen** (ID50 <1 .mu.M, with DCBN at 30 .mu.M), but only marginally by 4-methylpyrazole, an inhibitor of CYP2E1. In contrast, the activity of **CYP2A6** was only weakly inhibited by metyrapone or **methoxsalen** (ID50 >50 .mu.M). Thus, rat CYP2A3 and human **CYP2A6** have differences in substrate specificity as well as tissue distribution. These findings should be taken into account when assessing the risk of exposure to potential nasal toxicants in humans.

IT Chemicals
Nose
Toxicity
(baculovirus-mediated expression and characterization of rat CYP2A3 and human **CYP2A6** and metabolic activation of nasal toxicants)

IT Virus, animal
(baculo-, baculovirus-mediated expression and characterization of rat CYP2A3 and human **CYP2A6** and metabolic activation of nasal toxicants)

IT 58-22-0, Testosterone 91-64-5, Coumarin 100-02-7, 4-Nitrophenol, biological studies 680-31-9, Hexamethylphosphoramide, biological studies 1194-65-6, 2,6-Dichlorobenzonitrile
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(baculovirus-mediated expression and characterization of rat CYP2A3 and human **CYP2A6** and metabolic activation of nasal toxicants)

IT 2226-70-2, 15.alpha.-Hydroxytestosterone
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(baculovirus-mediated expression and characterization of rat CYP2A3 and human **CYP2A6** and metabolic activation of nasal toxicants)

IT 9035-51-2, Cytochrome P 450, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(isoforms; baculovirus-mediated expression and characterization of rat CYP2A3 and human **CYP2A6** and metabolic activation of nasal toxicants)

L22 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB We evaluated the specificity of 15 substrates and 14 inhibitors of the cytochrome P450s using nine human P 450 isoforms expressed in HepG2 cells using a recombinant vaccinia virus and also in human liver microsomes. Coumarin, 7-ethoxyresorufin, 7-benzyloxyresorufin, tolbutamide, aniline and diazepam were isoform-selective substrates towards **CYP2A6**, the CYP1A subfamily, CYP2B6, the CYP2C subfamily, CYP2E1 and the CYP3A subfamily, resp. However, a selective substrate for CYP2D6 was not found among the chems. tested. SKF-525A inhibited > 40% of the metabolic activity of all substrates tested, and the inhibitory effects differed among P 450 isoforms. Sulfaphenazole, 7,8-benzoflavone, quinidine and troleandomycin were selective inhibitors of the CYP2C subfamily (except CYP2C19), the CYP1A subfamily, CYP2D6 and the CYP3A subfamily, resp. **Methoxsalen** (**CYP2A6** inhibitor) inhibited the metabolic activity of CYP1A2 as well as that of **CYP2A6**. Diethyldithiocarbamate (CYP2E1 inhibitor) inhibited the metabolic activities of **CYP2A6** and CYP2C19 in addn. to that of CYP2E1. Our results indicated that substrates and inhibitors reported as P 450 selective probes are not necessarily specific for individual human P 450 isoforms. These results may provide useful information regarding human P 450 substrates and inhibitors in vitro using human liver microsomal

samples.

ACCESSION NUMBER: 1996:424712 CAPLUS
DOCUMENT NUMBER: 125:80284
TITLE: Specificity of substrate and inhibitor probes for cytochrome P450s: evaluation of in vitro metabolism using cDNA-expressed human P450s and human liver microsomes
AUTHOR(S): Ono, S.; Hatanaka, T.; Hotta, H.; Satoh, T.; Gonzalez, F. J.; Tsutsui, M.
CORPORATE SOURCE: Amersham K.K., Central Lab. for Research and Development, Chiba, 270-14, Japan
SOURCE: Xenobiotica (**1996**), 26(7), 681-693
CODEN: XENOBH; ISSN: 0049-8254
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Xenobiotica (**1996**), 26(7), 681-693
CODEN: XENOBH; ISSN: 0049-8254
AB We evaluated the specificity of 15 substrates and 14 inhibitors of the cytochrome P450s using nine human P 450 isoforms expressed in HepG2 cells using a recombinant vaccinia virus and also in human liver microsomes. Coumarin, 7-ethoxyresorufin, 7-benzyloxyresorufin, tolbutamide, aniline and diazepam were isoform-selective substrates towards **CYP2A6**, the CYP1A subfamily, CYP2B6, the CYP2C subfamily, CYP2E1 and the CYP3A subfamily, resp. However, a selective substrate for CYP2D6 was not found among the chems. tested. SKF-525A inhibited > 40% of the metabolic activity of all substrates tested, and the inhibitory effects differed among P 450 isoforms. Sulfaphenazole, 7,8-benzoflavone, quinidine and troleandomycin were selective inhibitors of the CYP2C subfamily (except CYP2C19), the CYP1A subfamily, CYP2D6 and the CYP3A subfamily, resp. **Methoxsalen** (**CYP2A6** inhibitor) inhibited the metabolic activity of CYP1A2 as well as that of **CYP2A6**. Diethyldithiocarbamate (CYP2E1 inhibitor) inhibited the metabolic activities of **CYP2A6** and CYP2C19 in addn. to that of CYP2E1. Our results indicated that substrates and inhibitors reported as P 450 selective probes are not necessarily specific for individual human P 450 isoforms. These results may provide useful information regarding human P 450 substrates and inhibitors in vitro using human liver microsomal samples.
IT 51-03-6, Piperonyl butoxide 56-54-2, Quinidine 62-68-0, SKF-525A 117-39-5, Quercetin 147-84-2, biological studies 155-09-9, Tranylcypromine **298-81-7**, **Methoxsalen** 519-23-3, Ellipticine 526-08-9, Sulfaphenazole 604-59-1, 7,8-Benzoflavone 2751-09-9, Troleandomycin 7554-65-6, 4-Methylpyrazole 65277-42-1, Ketoconazole 80288-49-9, Furafylline
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(specificity of substrate and inhibitor probes for cytochrome P 450 isoforms)

L22 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2002 ACS
AB Human exposure to polycyclic arom. hydrocarbons (PAHs) has been detd. by measurement of DNA adducts in human tissues. Competitive enzyme-linked immunosorbent assays (ELISAs) using antisera recognizing benzo[a]pyrene-diol-epoxide-modified DNA (BPDE-I-DNA) and color or fluorescence endpoint detection have been used extensively for quantifying PAH-DNA adducts. The fluorescence ELISA (limit of detection 1 adduct/108 nucleotides) was previously reported to be more sensitive than the color ELISA (1/107) for measuring PAH adducts (1988). However, the fluorescence

assay has the disadvantages of greater variation among the replicates and higher background levels than the color assay. Using a newly developed antiserum against BPDE-I-DNA, we have modified the color ELISA so that it has the same sensitivity as the fluorescence ELISA and requires only 33% of the sample quantity needed for the fluorescence ELISA. The modifications included preincubation of the antiserum with the samples, using microtiter plates with half-size, flat bottom wells, and optimizing the assay conditions. The improved color ELISA was used to analyze DNA samples from human autopsy tissues, including heart, lung, liver, kidney, spleen, pancreas and stomach from smokers and nonsmokers. With the exception of spleen and stomach, all tissues from smokers showed higher PAH-DNA adducts (ranging from 0.3 to 19.0 adducts/107 nucleotides) than the tissues from the nonsmokers (0.3 to 3.7 adducts/107 nucleotides) in two sep. expts. Among the tissues from smokers, heart showed the highest level of DNA adducts. This study demonstrates that a stable color ELISA with high sensitivity can be useful in assessing human exposure to PAH.

ACCESSION NUMBER: 1996:251865 CAPLUS
DOCUMENT NUMBER: 124:335049
TITLE: A sensitive color ELISA for detecting polycyclic aromatic hydrocarbon-DNA adducts in human tissues
AUTHOR(S): Mumford, Judy L.; Williams, Katherine; Wilcosky, Timothy C.; Everson, Richard B.; Young, Tielan L.; Santella, Regina M.
CORPORATE SOURCE: US EPA, Research Triangle Park, NC, 27711, USA
SOURCE: Mutat. Res. (**1996**), 359(3), 171-7
CODEN: MUREAV; ISSN: 0027-5107
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Mutat. Res. (**1996**), 359(3), 171-7
CODEN: MUREAV; ISSN: 0027-5107
IT Heart
Kidney
Liver
Lung
Pancreas
Spleen
Stomach
Tobacco smoke and **smoking**
(ELISA for detecting polycyclic arom. hydrocarbon-DNA adducts in human tissues)
IT **298-81-7D**, 8-Methoxypsoralen, DNA adducts 1162-65-8D, Aflatoxin b1, DNA adducts 60268-85-1D, DNA adduct 61490-67-3D, DNA adducts 63038-83-5D, DNA adducts 64938-66-5D, DNA adducts 114451-07-9D, DNA adducts
RL: ANT (Analyte); BPR (Biological process); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(ELISA for detecting polycyclic arom. hydrocarbon-DNA adducts in human tissues)

L22 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2002 ACS
AB **Methoxsalen** (8-methoxypsoralen) inhibited in vivo coumarin metab. in humans. **Methoxsalen** was metabolized in human liver microsomes at the rate of 50-100 pmol/mg protein/min. The metab. was not inhibited by the anti-Cyp2a-5 antibody in human liver microsomes and NIH 3T3 cells stably expressing catalytically active **CYP2A6** enzyme did not metabolize **methoxsalen**. **Methoxsalen** does not appear to be a substrate of **CYP2A6**. In pyrazole induced mouse liver microsomes, **methoxsalen** metab. was inhibited by the

anti-Cyp2a-5 antibody. Cyp2a-5 expressed in the yeast was capable of metabolizing **methoxsalen**, indicating that **methoxsalen** is a substrate of Cyp2a-5.

ACCESSION NUMBER: 1995:430167 CAPLUS
DOCUMENT NUMBER: 122:230042
TITLE: Coumarin and **methoxsalen** metabolism by **CYP2A6** and CYP2a-5 isoforms in man and mouse
AUTHOR(S): Maenpaa, Jukka; Juvonen, Risto; Raunio, Hannu; Rautio, Arja; Pelkonen, Olavi
CORPORATE SOURCE: Department Pharmacology and Toxicology, University Oulu, Oulu, 90220, Finland
SOURCE: Cytochrome P450 Int. Conf., 8th (**1994**), Meeting Date 1993, 631-4. Editor(s): Lechner, Maria Celeste. Libbey: Montrouge, Fr.
CODEN: 61COAX
DOCUMENT TYPE: Conference
LANGUAGE: English

TI Coumarin and **methoxsalen** metabolism by **CYP2A6** and CYP2a-5 isoforms in man and mouse

SO Cytochrome P450 Int. Conf., 8th (**1994**), Meeting Date 1993, 631-4. Editor(s): Lechner, Maria Celeste. Publisher: Libbey, Montrouge, Fr.
CODEN: 61COAX

AB **Methoxsalen** (8-methoxypsoralen) inhibited in vivo coumarin metab. in humans. **Methoxsalen** was metabolized in human liver microsomes at the rate of 50-100 pmol/mg protein/min. The metab. was not inhibited by the anti-Cyp2a-5 antibody in human liver microsomes and NIH 3T3 cells stably expressing catalytically active **CYP2A6** enzyme did not metabolize **methoxsalen**. **Methoxsalen** does not appear to be a substrate of **CYP2A6**. In pyrazole induced mouse liver microsomes, **methoxsalen** metab. was inhibited by the anti-Cyp2a-5 antibody. Cyp2a-5 expressed in the yeast was capable of metabolizing **methoxsalen**, indicating that **methoxsalen** is a substrate of Cyp2a-5.

ST **methoxsalen** coumarin metab cytochrome P 450

IT Liver
Microsome
(coumarin and **methoxsalen** metab. by cytochrome P 450 **CYP2A6** and CYP2a-5 isoforms in man and mouse)

IT **298-81-7**, **Methoxsalen**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(coumarin and **methoxsalen** metab. by cytochrome P 450 **CYP2A6** and CYP2a-5 isoforms in man and mouse)

IT 91-64-5, Coumarin
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(coumarin and **methoxsalen** metab. by cytochrome P 450 **CYP2A6** and CYP2a-5 isoforms in man and mouse)

L22 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB **Methoxsalen** (8-methoxypsoralen) is a very potent inhibitor of human cytochrome P 450 2A6 (**CYP2A6**) and mouse Cyp2a-5-mediated coumarin 7-hydroxylation in vitro. To det. the effect of **methoxsalen** on coumarin 7-hydroxylation in humans in vivo, five subjects were given 45 mg of **methoxsalen** and 5 mg of coumarin. **Methoxsalen** inhibited in vivo coumarin metab. by 47 .+-. 9.2% (mean .+-. SEM). **Methoxsalen** was metabolized in human liver microsomes at the rate of 50-100 pmol/mg protein/min (approx. 30% of the

activity in mouse liver microsomes). Metab. was not inhibited by the anti-Cyp2a-5 antibody in human liver microsomes. NIH 3T3 cells stably expressing catalytically active **CYP2A6** enzyme did not metabolize **methoxsalen**, indicating that **CYP2A6** does not accept **methoxsalen** as a substrate. In pyrazole-induced mouse liver microsomes, **methoxsalen** metab. was inhibited by the anti-Cyp2a-5 antibody. Cyp2a-5 protein expressed in the yeast Saccharomyces cerevisiae was capable of metabolizing **methoxsalen**, indicating that **methoxsalen** is a substrate of Cyp2a-5. Although kinetic studies indicated that the inhibition of coumarin 7-hydroxylation by **methoxsalen** is competitive in human liver microsomes, **methoxsalen** does not appear to be a substrate for **CYP2A6**. **Methoxsalen** and coumarin have the potential of strong metabolic interactions in man.

ACCESSION NUMBER: 1994:671322 CAPLUS
DOCUMENT NUMBER: 121:271322
TITLE: Metabolic interactions of **methoxsalen** and coumarin in humans and mice
AUTHOR(S): Maenpaa, Jukka; Juvonen, Risto; Raunio, Hannu; Rautio, Arja; Pelkonen, Olavi
CORPORATE SOURCE: Dep. Pharmacol. and Toxicol., Univ. Oulu, Oulu, SF-90220, Finland
SOURCE: Biochem. Pharmacol. (**1994**), 48(7), 1363-9
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Metabolic interactions of **methoxsalen** and coumarin in humans and mice

SO Biochem. Pharmacol. (**1994**), 48(7), 1363-9
CODEN: BCPCA6; ISSN: 0006-2952

AB **Methoxsalen** (8-methoxypsoralen) is a very potent inhibitor of human cytochrome P 450 2A6 (**CYP2A6**) and mouse Cyp2a-5-mediated coumarin 7-hydroxylation in vitro. To det. the effect of **methoxsalen** on coumarin 7-hydroxylation in humans in vivo, five subjects were given 45 mg of **methoxsalen** and 5 mg of coumarin. **Methoxsalen** inhibited in vivo coumarin metab. by 47 .+-. 9.2% (mean .+-. SEM). **Methoxsalen** was metabolized in human liver microsomes at the rate of 50-100 pmol/mg protein/min (approx. 30% of the activity in mouse liver microsomes). Metab. was not inhibited by the anti-Cyp2a-5 antibody in human liver microsomes. NIH 3T3 cells stably expressing catalytically active **CYP2A6** enzyme did not metabolize **methoxsalen**, indicating that **CYP2A6** does not accept **methoxsalen** as a substrate. In pyrazole-induced mouse liver microsomes, **methoxsalen** metab. was inhibited by the anti-Cyp2a-5 antibody. Cyp2a-5 protein expressed in the yeast Saccharomyces cerevisiae was capable of metabolizing **methoxsalen**, indicating that **methoxsalen** is a substrate of Cyp2a-5. Although kinetic studies indicated that the inhibition of coumarin 7-hydroxylation by **methoxsalen** is competitive in human liver microsomes, **methoxsalen** does not appear to be a substrate for **CYP2A6**. **Methoxsalen** and coumarin have the potential of strong metabolic interactions in man.

ST drug interaction **methoxsalen** coumarin

IT Drug interactions
(metabolic, metabolic interactions of **methoxsalen** and coumarin in humans and mice)

IT 9035-51-2, Cytochrome p450, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological

process); BIOL (Biological study); PROC (Process)
(CYP2 isoenzymes; metabolic interactions of **methoxsalen** and coumarin in humans and mice)

IT 91-64-5, Coumarin **298-81-7**, **Methoxsalen**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(metabolic interactions of **methoxsalen** and coumarin in humans and mice)

L22 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB The definition for a chem. carcinogen is given, and the data on oncol. morbidity and the up-to-date classifications of chem. carcinogens are presented, including the list of abs. carcinogens (group I according to the International Agency on Cancer Research) and the national (Russian) list of carcinogenic factors.

ACCESSION NUMBER: 1994:611699 CAPLUS
DOCUMENT NUMBER: 121:211699
TITLE: Chemical carcinogens in the environment and their ecological significance. Classification principles
AUTHOR(S): Khudolei, V. V.; Filov, V. A.
CORPORATE SOURCE: NII Onkol., St.-Petersburg, 189646, Russia
SOURCE: Zh. Ekol. Khim. (**1993**), (2), 145-9
CODEN: ZEKHE6; ISSN: 0869-3498
DOCUMENT TYPE: Journal
LANGUAGE: Russian

SO Zh. Ekol. Khim. (**1993**), (2), 145-9
CODEN: ZEKHE6; ISSN: 0869-3498

IT Alcoholic beverages
Dyes
Soot
Tobacco smoke and **smoking**
(carcinogen; chem. carcinogens in environment and their ecol. significance and classification principles)

IT 55-98-1, Mileran 56-53-1, Diethylstilbestrol 71-43-2, Benzene, biological studies 75-01-4, Vinyl chloride, biological studies 91-59-8, 2-Naphthylamine 92-67-1, 4-Aminobiphenyl 92-87-5, Benzidene 148-82-3, Melphalan **298-81-7**, Methoxalen 446-86-6, Azathioprin 494-03-1, Chlornaphazin 505-60-2, Mustard gas 542-88-1, Bis(chloromethyl) ether
RL: ADV (Adverse effect, including toxicity); POL (Pollutant); BIOL (Biological study); OCCU (Occurrence)
(carcinogen; chem. carcinogens in the environment and their ecol. significance. Classification principles)

L22 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB Parsley is known to respond to UV irradn. by the synthesis of flavone glycosides, whereas fungal or elicitor stress leads to the synthesis of furanocoumarin phytoalexins. The authors tested how these defensive pathways are affected by a single ozone treatment (200 nL L-1; 10 h). Assays were performed at the levels of transcripts, for enzyme activities, and for secondary products. The most rapid transcript accumulation was maximal at 3 h, whereas flavone glycosides and furanocoumarins were maximally induced at 12 and 24 h, resp., after the start of ozone treatment. Ozone acted as a cross-inducer because the 2 distinct pathways were simultaneously induced. These results are consistent with the previously obsd. ozone induction of fungal and viral defense reactions in **tobacco**, spruce, and pine.

ACCESSION NUMBER: 1994:156150 CAPLUS
DOCUMENT NUMBER: 120:156150

09/214,851

TITLE: Biochemical plant responses to ozone. IV. Cross-induction of defensive pathways in parsley (Petroselinum crispum L.) plants

AUTHOR(S): Eckey-Kaltenbach, Heidrun; Ernst, Dieter; Heller, Werner; Sandermann, Heinrich, Jr.

CORPORATE SOURCE: Inst. Biochem. Pflanzenpathol., Forschungszen. Umwelt und Gesundheit GmbH, Oberschleissheim, D-85758, Germany

SOURCE: Plant Physiol. (**1994**), 104(1), 67-74
CODEN: PLPHAY; ISSN: 0032-0889

DOCUMENT TYPE: Journal

LANGUAGE: English

SO Plant Physiol. (**1994**), 104(1), 67-74
CODEN: PLPHAY; ISSN: 0032-0889

AB Parsley is known to respond to UV irradn. by the synthesis of flavone glycosides, whereas fungal or elicitor stress leads to the synthesis of furanocoumarin phytoalexins. The authors tested how these defensive pathways are affected by a single ozone treatment (200 nL L-1; 10 h). Assays were performed at the levels of transcripts, for enzyme activities, and for secondary products. The most rapid transcript accumulation was maximal at 3 h, whereas flavone glycosides and furanocoumarins were maximally induced at 12 and 24 h, resp., after the start of ozone treatment. Ozone acted as a cross-inducer because the 2 distinct pathways were simultaneously induced. These results are consistent with the previously obsd. ozone induction of fungal and viral defense reactions in **tobacco**, spruce, and pine.

IT 66-97-7, Psoralen 93-35-6, Umbelliferone **298-81-7**, Xanthotoxin 482-27-9, Isopimpinellin 484-20-8, Bergapten
RL: BIOL (Biological study)
(of parsley leaf, after ozone exposure)

L22 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB Five insecticide synergists, all of which were either methylenedioxyphenyl compds. or analogs, were compared as to their effect on cytochrome P 450 monooxygenase induction caused by an allelochem. in fall armyworm larvae. Feeding the synergists (piperonyl butoxide, safrole, isosafrole, MGK 264, and myristicin) individually to the larvae caused decreases in the microsomal aldrin epoxidase activities ranging from 38 to 74% when compared with controls. Feeding indole-3-carbinol resulted in a 4-fold increase in the microsomal epoxidase activity. However, cotreatment of any of the synergists and the inducer completely eliminated the induction. Sixth instar larvae were more inducible than second instar larvae with respect to microsomal epoxidase and glutathione transferase in the fall armyworm. Enzyme inducibility varied widely among the seven phytophagous Lepidoptera examd. When indole-3-carbinol was used as an inducer of microsomal epoxidase, the extent of inducibility of the enzyme was as follows: fall armyworm > velvetbean caterpillar > corn earworm > beet armyworm > **tobacco** budworm > cabbage looper > diamond back moth. When indole-3-acetonitrile was used as an inducer, the inducibility of glutathione transferase was the following: fall armyworm > beet armyworm > corn earworm > cabbage looper > velvetbean caterpillar > **tobacco** budworm > diamondback moth. Inducibility of five microsomal oxidase systems also varied considerably in the corn earworm, indicating the multiplicity of cytochrome P 450 in this species. Microsomal epoxidase and glutathione transferase were induced by cruciferous host plants such as cabbage and their allelochems. in diamondback moth larvae.

ACCESSION NUMBER: 1993:643577 CAPLUS

DOCUMENT NUMBER: 119:243577

09/214,851

TITLE: Induction of detoxification enzymes in phytophagous insects: roles of insecticide synergists, larval age, and species

AUTHOR(S): Yu, Simon J.; Hsu, Err L.

CORPORATE SOURCE: Dep. Entomol. Nematol., Univ. Florida, Gainesville, FL, 32611, USA

SOURCE: Arch. Insect Biochem. Physiol. (1993), 24(1), 21-32
CODEN: AIBPEA; ISSN: 0739-4462

DOCUMENT TYPE: Journal

LANGUAGE: English

SO Arch. Insect Biochem. Physiol. (1993), 24(1), 21-32
CODEN: AIBPEA; ISSN: 0739-4462

AB Five insecticide synergists, all of which were either methylenedioxyphenyl compds. or analogs, were compared as to their effect on cytochrome P 450 monooxygenase induction caused by an allelochem. in fall armyworm larvae. Feeding the synergists (piperonyl butoxide, safrole, isosafrole, MGK 264, and myristicin) individually to the larvae caused decreases in the microsomal aldrin epoxidase activities ranging from 38 to 74% when compared with controls. Feeding indole-3-carbinol resulted in a 4-fold increase in the microsomal epoxidase activity. However, cotreatment of any of the synergists and the inducer completely eliminated the induction. Sixth instar larvae were more inducible than second instar larvae with respect to microsomal epoxidase and glutathione transferase in the fall armyworm. Enzyme inducibility varied widely among the seven phytophagous Lepidoptera examd. When indole-3-carbinol was used as an inducer of microsomal epoxidase, the extent of inducibility of the enzyme was as follows: fall armyworm > velvetbean caterpillar > corn earworm > beet armyworm > **tobacco** budworm > cabbage looper > diamond back moth. When indole-3-acetonitrile was used as an inducer, the inducibility of glutathione transferase was the following: fall armyworm > beet armyworm > corn earworm > cabbage looper > velvetbean caterpillar > **tobacco** budworm > diamondback moth. Inducibility of five microsomal oxidase systems also varied considerably in the corn earworm, indicating the multiplicity of cytochrome P 450 in this species. Microsomal epoxidase and glutathione transferase were induced by cruciferous host plants such as cabbage and their allelochems. in diamondback moth larvae.

IT 57-06-7 89-78-1, Menthol **298-81-7**, Xanthotoxin 3952-98-5, Sinigrin
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(detoxification enzymes of diamondback moth response to)

L22 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB Coumarin is 7-hydroxylated by cytochrome P 450 isoform Cyp2a-5 in mice and **CYP2A6** in humans. Various drugs, endogenous substances, plant substances and carcinogens, altogether .apprx.90 chems., were evaluated as possible inhibitors of coumarin 7-hydroxylase (I) activity in mouse microsomes. The effects of selected compds. on I activity in human liver microsomes were also tested. The furanocoumarin derivs., **methoxsalen** (8-methoxypsoralen) and psoralen, proved to be the most potent inhibitors of mouse I activity (IC50 = 1.0 and 3.1 .mu.M, resp.). The furanocoumarins, bergapten (5-methoxypsoralen), isopimpinellin (5,8-dimethoxypsoralen), imperatorin, and sphondin, also effectively inhibited mouse I activity (IC50 = 19-40 .mu.M). **Methoxsalen**, isopimpinellin and metyrapone were also inhibitors in mice in vivo. **Methoxsalen** was a potent inhibitor of I activity also in human liver microsomes (IC50 = 5.4 .mu.M), whereas bergapten,

isopimpinellin and imperatorin had no effect. The imidazole antimycotic miconazole was a potent but nonspecific inhibitor of I activity. Several known substrates and inhibitors of members in the CYP1A, CYP2B, CYP2C, CYP2D and CYP3A subfamilies were poor inhibitors of I activity. These results suggested that (1) the coumarin-type compds. in particular interact with the active sites of Cyp2a-5 and **CYP2A6**, and (2) the active sites of Cyp2a-5 and **CYP2A6** are structurally different, since a no. of compds. inhibited mouse, but not human I activity.

ACCESSION NUMBER: 1993:250399 CAPLUS
DOCUMENT NUMBER: 118:250399
TITLE: Differential inhibition of coumarin 7-hydroxylase activity in mouse and human liver microsomes
AUTHOR(S): Maenpaa, Jukka; Sigusch, Holger; Raunio, Hannu; Syngelma, Tuula; Vuorela, Pia; Vuorela, Heikki; Pelkonen, Olavi
CORPORATE SOURCE: Dep. Pharmacol. Toxicol., Univ. Oulu, Oulu, SF-90220, Finland
SOURCE: Biochem. Pharmacol. (**1993**), 45(5), 1035-42
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Biochem. Pharmacol. (**1993**), 45(5), 1035-42
CODEN: BCPCA6; ISSN: 0006-2952

AB Coumarin is 7-hydroxylated by cytochrome P 450 isoform Cyp2a-5 in mice and **CYP2A6** in humans. Various drugs, endogenous substances, plant substances and carcinogens, altogether .apprx.90 chems., were evaluated as possible inhibitors of coumarin 7-hydroxylase (I) activity in mouse microsomes. The effects of selected compds. on I activity in human liver microsomes were also tested. The furanocoumarin derivs., **methoxsalen** (8-methoxypsoralen) and psoralen, proved to be the most potent inhibitors of mouse I activity (IC50 = 1.0 and 3.1 .mu.M, resp.). The furanocoumarins, bergapten (5-methoxypsoralen), isopimpinellin (5,8-dimethoxypsoralen), imperatorin, and sphondin, also effectively inhibited mouse I activity (IC50 = 19-40 .mu.M). **Methoxsalen**, isopimpinellin and metyrapone were also inhibitors in mice in vivo. **Methoxsalen** was a potent inhibitor of I activity also in human liver microsomes (IC50 = 5.4 .mu.M), whereas bergapten, isopimpinellin and imperatorin had no effect. The imidazole antimycotic miconazole was a potent but nonspecific inhibitor of I activity. Several known substrates and inhibitors of members in the CYP1A, CYP2B, CYP2C, CYP2D and CYP3A subfamilies were poor inhibitors of I activity. These results suggested that (1) the coumarin-type compds. in particular interact with the active sites of Cyp2a-5 and **CYP2A6**, and (2) the active sites of Cyp2a-5 and **CYP2A6** are structurally different, since a no. of compds. inhibited mouse, but not human I activity.

IT 9035-51-2, Cytochrome P 450, properties
RL: PRP (Properties)
(**CYP2A6** and Cyp2a-5, of human and mouse liver microsomes, differential inhibition of, by furocoumarins and other compds., inhibitor structure in relation to)

IT 50-02-2, Dexamethasone 50-12-4, Mephenytoin 50-18-0, Cyclophosphamide 50-28-2, Estradiol, biological studies 50-32-8, Benzo[a]pyrene, biological studies 50-33-9, Phenylbutazone, biological studies 50-36-2, Cocaine 51-45-6, Histamine, biological studies 52-53-9, Verapamil 54-31-9, Furosemide 54-36-4, Metyrapone 55-18-5, Diethylnitrosamine 56-54-2, Quinidine 57-41-0, Phenytoin 57-42-1,

Meperidine 57-83-0, Progesterone, biological studies 57-88-5, Cholesterol, biological studies 58-08-2, Caffeine, biological studies 58-22-0, Testosterone 58-27-5, Menadione 58-55-9, Theophylline, biological studies 60-80-0, Antipyrine 62-53-3, Aniline, biological studies 62-68-0, SKF 525A 62-75-9, Dimethylnitrosamine 63-91-2, Phenylalanine, biological studies 64-77-7, Tolbutamide 66-76-2 66-97-7, Psoralen 67-97-0, Vitamin D3 71-58-9, Medroxyprogesterone acetate 77-21-4, Glutethimide 81-81-2, Warfarin 82-02-0, Khellin 83-67-0, Theobromine 90-15-3, 1-Naphthol 90-39-1, Sparteine 95-25-0, Chlorzoxazone 117-39-5, Quercetin 125-84-8, Aminoglutethimide 130-95-0, Quinine 131-12-4, Pimpinellin 137-58-6, Lidocaine 288-13-1, Pyrazole 288-32-4, Imidazole, biological studies 298-46-4, Carbamazepine **298-81-7**, **Methoxsalen** 303-81-1, Novobiocin 443-48-1, Metronidazole 482-27-9, Isopimpinellin 482-44-0, Imperatorin 482-48-4, Isobergapten 483-66-9, Sphondin 484-20-8, Bergapten 521-35-7, Cannabinol 523-50-2, Angelicin 525-66-6 604-59-1, .alpha.-Naphthoflavone 621-82-9, Cinnamic acid, biological studies 642-08-0 846-50-4, Temazepam 1131-64-2, Debrisoquine 1162-65-8, Aflatoxin B1 1672-63-5, 4-Hydroxyantipyrine 3469-69-0, 4-Iodopyrazole 5058-13-9, Columbianadin 5104-49-4, Flurbiprofen 5522-43-0, 1-Nitropyrene 7554-65-6, 4-Methylpyrazole 10238-21-8, Glibenclamide 11104-38-4, Vitamin K1 13292-46-1, Rifampicin 13956-29-1, Cannabidiol 15687-27-1, Ibuprofen 20830-75-5, Digoxin 21829-25-4, Nifedipine 22071-15-4, Ketoprofen 22916-47-8, Miconazole 23593-75-1, Clotrimazole 42399-41-7, Diltiazem 51481-61-9, Cimetidine 53947-89-0, Apterin 59865-13-3, Cyclosporin A 62571-86-2, Captopril 75695-93-1, Isradipine
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(coumarin hydroxylase of human and mouse liver microsomes response to, structure in relation to)

L22 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB The CASE (Computer Automated Structure Evaluation) structure-activity methodol. has been applied to a Gene-Tox derived Salmonella mutagenicity data base consisting of 808 chems. Based upon qual. structural features, CASE identified 29 activating and 3 inactivating structural determinants which correctly predicted the probability of carcinogenicity of 93.7% of the known mutagens and nonmutagens in the data base (sensitivity = 0.998, and specificity = 0.704). Addnl., based upon a qual. structure-activity anal., CASE's performance was even better, leading to a sensitivity of 0.981 and a specificity of 1.000. Using the structural determinants identified in this data base, CASE gave excellent predictions of the mutagenicity of chems. not included in the data base. The identified biophores and biophobes can also be used to investigate the structural basis of the mutagenicity of various chem. classes.

ACCESSION NUMBER:	1990:173827 CAPLUS
DOCUMENT NUMBER:	112:173827
TITLE:	The structural basis of the mutagenicity of chemicals in Salmonella typhimurium: The Gene-Tox data base
AUTHOR(S):	Klopman, Gilles; Frierson, Manton R.; Rosenkranz, Herbert S.
CORPORATE SOURCE:	Dep. Chem., Case West. Reserve Univ., Cleveland, OH, 44106, USA
SOURCE:	Mutat. Res. (**1990**), 228(1), 1-50 CODEN: MUREAV; ISSN: 0027-5107
DOCUMENT TYPE:	Journal
LANGUAGE:	English

SO Mutat. Res. (1990), 228(1), 1-50
CODEN: MUREAV; ISSN: 0027-5107

IT 50-06-6, Phenobarbital, biological studies 50-07-7, Mitomycin C 50-18-0, Cyclophosphamide 50-29-3, biological studies 50-32-8, Benzo[a]pyrene, biological studies 50-33-9, Phenylbutazone, biological studies 50-44-2, 6-Mercaptopurine 50-81-7, L-Ascorbic acid, biological studies 51-21-8, 5-Fluorouracil 51-34-3, Scopolamine 51-55-8, Atropine, biological studies 51-79-6, Urethane 52-24-4, Thio-TEPA 52-68-6, Trichlorfon 53-70-3, Dibenz[a,h]anthracene 53-94-1, N-Hydroxy-2-aminofluorene 53-95-2, N-Hydroxy-2-acetylaminofluorene 53-96-3 54-11-5, **Nicotine** 54-31-9, Furosemide 54-42-2, 5-Iododeoxyuridine 54-88-6 55-18-5, Diethylnitrosamine 55-38-9, Fenthion 55-86-7, Nitrogen mustard 56-23-5, Carbon tetrachloride, biological studies 56-38-2, Ethyl parathion 56-49-5, 3-Methylcholanthrene 56-53-1, Diethylstilbestrol 56-55-3, Benz[a]anthracene 56-57-5, 4-Nitroquinoline-1-oxide 56-75-7, Chloramphenicol 57-14-7, 1,1-Dimethylhydrazine 57-57-8, .beta.-Propiolactone 57-67-0, Sulfaguanidine 57-94-3 57-97-6 58-08-2, biological studies 58-14-0 58-25-3, Chlordiazepoxide 58-93-5, Hydrochlorothiazide 58-94-6, Chlorothiazide 59-05-2, Methotrexate 59-46-1 59-87-0, Nitrofurazone 59-89-2, N-Nitrosomorpholine 60-00-4, biological studies 60-09-3, 4-Aminoazobenzene 60-11-7, p-Dimethylaminoazobenzene 60-23-1, Cysteamine 60-29-7, Diethyl ether, biological studies 60-34-4, Methylhydrazine 60-35-5, Acetamide, biological studies 60-54-8, Tetracycline 60-57-1, Dieldrin 60-80-0 61-33-6, Penicillin G, biological studies 61-57-4, Niridazole 61-73-4, Methylene blue 61-82-5, Amitrole 62-23-7 62-50-0, Ethyl methanesulfonate 62-53-3, Aniline, biological studies 62-55-5, Ethanethioamide 62-56-6, Thiourea, biological studies 62-73-7, Dichlorvos 62-75-9, Dimethylnitrosamine 63-25-2, Carbaryl 64-17-5, Ethanol, biological studies 64-19-7, Acetic acid, biological studies 64-67-5, Diethyl sulfate 65-61-2, Acridine orange 65-85-0, Benzoic acid, biological studies 66-27-3, Methyl methanesulfonate 66-75-1, Uracil mustard 67-20-9, Nitrofurantoin 67-64-1, Acetone, biological studies 67-68-5, Dimethyl sulfoxide, biological studies 67-72-1, Hexachloroethane 69-72-7, Salicylic acid, biological studies 70-25-7, MNNG 71-36-3, 1-Butanol, biological studies 72-20-8, Endrin 72-43-5, Methoxychlor 72-55-9, biological studies 72-57-1, C.I. Direct blue 14 75-01-4, biological studies 75-09-2, Methylene chloride, biological studies 75-21-8, Oxirane, biological studies 75-35-4, Vinylidene chloride, biological studies 75-55-8, Propylenimine 75-89-8, 2,2,2-Trifluoroethanol 75-90-1, Trifluoroacetaldehyde 76-03-9, Trichloroacetic acid, biological studies 76-05-1, Trifluoroacetic acid, biological studies 76-38-0, Methoxyflurane 76-44-8, Heptachlor 76-60-8, Bromocresol green 77-06-5, Gibberellic acid 77-78-1, Dimethyl sulfate 78-87-5, Propylene chloride 78-88-6, 2,3-Dichloro-1-propene 79-01-6, Trichloroethylene, biological studies 79-11-8, Chloroacetic acid, biological studies 79-44-7, Dimethylcarbamoyl chloride 80-40-0, Ethyl p-toluenesulfonate 81-07-2, Saccharin 81-88-9, Rhodamine b 82-68-8, Pentachloronitrobenzene 84-86-6, 4-Amino-1-naphthalenesulfonic acid 84-88-8 85-01-8, Phenanthrene, biological studies 85-02-9, .beta.-Naphthoquinoline 85-81-4, 6-Methoxy-8-nitroquinoline 85-83-6, Scarlet red 86-30-6, Diphenylnitrosamine 86-50-0, Azinphos-methyl 86-73-7, Fluorene 86-95-3, 2,4-Dihydroxyquinoline 86-98-6, 4,7-Dichloroquinoline 87-86-5, Pentachlorophenol 88-06-2, 2,4,6-Trichlorophenol 88-19-7, o-Toluenesulfonamide 88-85-7 89-73-6, Salicylhydroxamic acid 90-05-1, Guaiacol 90-15-3, 1-Naphthol 90-30-2

90-41-5, 2-Aminobiphenyl 90-45-9, 9-Aminoacridine 90-65-3, Penicillic acid 91-20-3, Naphthalene, biological studies 91-22-5, Quinoline, biological studies 91-23-6, o-Nitroanisole 91-53-2, Ethoxyquine 91-59-8, 2-Naphthylamine 91-62-3, 6-Methylquinoline 91-63-4, Quinaldine 91-94-1, 3,3'-Dichlorobenzidine 92-55-7, 5-Nitrofurfural diacetate 92-62-6, Proflavin 92-67-1, [1,1'-Biphenyl]-4-amine 92-87-5, Benzidine 92-93-3 93-10-7, Quinaldic acid 94-13-3, Propylparaben 94-24-6, Tetracaine 94-58-6, Dihydrosafrole 94-59-7 94-75-7, biological studies 94-82-6, 2,4-Dichlorophenoxybutyric acid 95-06-7, Sulfallate 95-53-4, o-Toluidine, biological studies 95-80-7, 2,4-Diaminotoluene 96-09-3, Styrene oxide 96-12-8, 1,2-Dibromo-3-chloropropane 96-23-1, 1,3-Dichloro-2-propanol 96-45-7, N,N'-Ethylenethiourea 97-56-3, o-Aminoazotoluene 98-01-1, Furfural, biological studies 98-07-7, Benzotrichloride 98-87-3, Benzal chloride 99-09-2, m-Nitroaniline 99-33-2, 3,5-Dinitrobenzoyl chloride 99-56-9, 4-Nitro-o-phenylenediamine 99-59-2, 5-Nitro-o-anisidine 99-65-0 100-02-7, p-Nitrophenol, biological studies 100-17-4, p-Nitroanisole 100-32-3, Bis(4-nitrophenyl) disulfide 100-42-5, biological studies 100-44-7, Benzyl chloride, biological studies 100-75-4, N-Nitrosopiperidine 101-14-4 101-54-2, N-Phenyl-p-phenylenediamine 103-30-0, trans-Stilbene 103-33-3, Azobenzene 103-84-4, Acetanilide 103-90-2 106-88-7, 1,2-Epoxybutane 106-89-8, biological studies 106-93-4, 1,2-Dibromoethane 107-06-2, 1,2-Dichloroethane, biological studies 107-07-3, Ethylene chlorohydrin, biological studies 107-13-1, 2-Propenenitrile, biological studies 107-20-0, 2-Chloroacetaldehyde 107-21-1, 1,2-Ethanediol, biological studies 108-05-4, Acetic acid ethenyl ester, biological studies 108-30-5, Succinic anhydride, biological studies 108-45-2, m-Phenylenediamine, biological studies 108-46-3, Resorcinol, biological studies 108-86-1, Bromobenzene, biological studies 109-84-2, N-(2-Hydroxyethyl)hydrazine 110-82-7, Cyclohexane, biological studies 115-02-6, Azaserine 115-20-8, 2,2,2-Trichloroethanol 115-90-2, Fensulfothion 116-63-2 116-83-6, 1-Amino-4-methoxyanthraquinone 116-85-8 117-39-5, Quercetin 117-62-4 118-96-7, 2,4,6-Trinitrotoluene 119-26-6, 2,4-Dinitrophenylhydrazine 119-27-7, 2,4-Dinitroanisole 119-65-3, Isoquinoline 119-90-4, 3,3'-Dimethoxybenzidine 120-12-7, Anthracene, biological studies 120-58-1, Isosafrole 121-75-5, Malathion 121-88-0, 2-Amino-5-nitrophenol 121-92-6, 3-Nitrobenzoic acid 122-34-9, Simazine 123-30-8 123-33-1 124-20-9, Spermidine 126-07-8 126-72-7 127-00-4, 1-Chloro-2-propanol 128-37-0, BHT, biological studies 129-00-0, Pyrene, biological studies 129-03-3, Cyproheptadine 130-16-5, 5-Chloro-8-hydroxyquinoline 133-06-2, Captan 133-07-3, Folpet 134-32-7, 1-Naphthylamine 134-90-7, L-(+)-threo-Chloramphenicol 137-58-6, Lidocaine 140-79-4, 1,4-Dinitrosopiperazine 145-48-2, 2-Quinizarinsulfonic acid 146-59-8, ICR 170 148-24-3, 8-Hydroxyquinoline, biological studies 148-82-3, Melphalan 149-29-1, Patulin 150-68-5, Monuron 150-70-9 151-56-4, Ethylenimine, biological studies 151-67-7 153-78-6, 2-Aminofluorene
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(mutagenicity of, Computer Automated Structure Evaluation for study of structural determinants in relation to)

IT 154-93-8 189-55-9, Dibenzo(a,i)pyrene 191-24-2, Benzo(ghi)perylene 191-26-4, Anthanthrene 192-97-2, Benzo(e)pyrene 215-58-7, Benzo[b]triphenylene 218-01-9, Chrysene 224-41-9, Dibenz(a,j)anthracene 224-42-0, Dibenz(a,j)acridine 229-87-8, Phenanthridine 298-00-0, Methyl parathion 298-02-2, Phorate 298-04-4, Disulfoton 298-46-4, Carbamazepine **298-81-7**, 8-Methoxypsoralen 302-17-0, Chloral hydrate 303-47-9, Ochratoxin A

303-53-7, Cyclobenzaprine 304-28-9, 2,7-Bis(acetylamino)fluorene 309-00-2, Aldrin 314-13-6 314-40-9, Bromacil 330-55-2, Linuron 333-20-0, Potassium thiocyanate 333-41-5, Diazinon 334-22-5 363-49-5 366-29-0 366-70-1, Natulan 406-90-6, Fluroxene 421-20-5, Methyl fluorosulfate 439-14-5 443-48-1 446-86-6, Azathioprine 475-54-7, Oosporein 476-43-7 476-46-0 478-08-0 479-50-5, Lucanthone 480-54-6, Retrorsine 481-72-1 483-84-1, Flavianic acid 491-35-0, Lepidine 493-52-7, Methyl red 494-03-1, Chlornaphazine 495-18-1, Benzohydroxamic acid 501-30-4, Kojic acid 502-44-3, 2-Oxepanone 518-75-2, Citrinin 521-61-9 521-62-0, Frangulin A 523-44-4, Orange I 525-47-3, 5-Nitroquinaldic acid 531-82-8 532-82-1, Chrysoidine 534-07-6, 1,3-Dichloroacetone 535-75-1, 2-Piperidinecarboxylic acid 540-51-2, 2-Bromoethanol 540-73-8, 1,2-Dimethylhydrazine 542-78-9, Malonaldehyde 547-58-0, Methyl orange 548-57-2, Miracil d 548-62-9, Crystal violet 549-34-8 550-60-7, 1-Nitro-2-naphthalenol 550-74-3, Picrolonic acid 551-06-4, 1-Naphthylisothiocyanate 551-92-8, Dimetridazole 552-16-9, 2-Nitrobenzoic acid 552-89-6, 2-Nitrobenzaldehyde 553-24-2, Neutral red 555-16-8, 4-Nitrobenzaldehyde, biological studies 555-30-6, Methyldopa 556-52-5, Oxiranemethanol 563-12-2, Ethion 568-75-2 569-61-9, Pararosaniline 573-89-7 578-66-5, 8-Aminoquinoline 581-89-5, 2-Nitronaphthalene 592-62-1, Methylazoxymethanol acetate 598-55-0, Methyl carbamate 602-87-9, 5-Nitroacenaphthene 607-30-7 607-34-1, 5-Nitroquinoline 607-35-2, 8-Nitroquinoline 607-57-8, 2-Nitrofluorene 610-49-1, 1-Anthramine 610-67-3, o-Nitrophenetole 611-09-6, 5-Nitroisatin 611-32-5, 8-Methylquinoline 612-23-7, o-Nitrobenzyl chloride 612-24-8, 2-Nitrobenzonitrile 612-58-8, 3-Methylquinoline 612-60-2, 7-Methylquinoline 612-62-4, 2-Chloroquinoline 613-13-8, 2-Anthramine 613-47-8, N-2-Naphthylhydroxylamine 613-50-3, 6-Nitroquinoline 614-95-9, N-Ethyl-N-nitrosourethane 615-05-4, 2,4-Diaminoanisole 615-53-2 621-64-7, Dipropylnitrosamine 624-76-0, 2-Iodoethanol 632-79-1, Tetrabromophthalic anhydride 645-12-5, 5-Nitro-2-furoic acid 684-93-5, 1-Methyl-1-nitrosourea 696-23-1, 2-Methyl-4-nitroimidazole 709-98-8, Propanil 710-25-8 720-69-4 759-73-9, 1-Ethyl-1-nitrosourea 765-34-4, Glycidaldehyde 772-43-0, 5-Nitro-2-furamidoxime 781-43-1, 9,10-Dimethylanthracene 790-60-3, Benz(a)anthracene-5,6-oxide 817-99-2, N-Diazoacetylglycine amide 820-75-7, N-Diazoacetylglycine hydrazide 826-81-3, 8-Hydroxy-2-methylquinoline 842-07-9, C.I. Solvent yellow 14 860-22-0, Indigo carmine 881-07-2, 8-Nitroquinaldine 892-17-1 915-67-3 924-16-3, Dibutylnitrosamine 930-55-2, 1-Nitrosopyrrolidine 937-40-6, Benzyl(methyl)nitrosamine 944-22-9, Fonofos 963-89-3, 7,9-Dimethylbenz(c)acridine 999-29-1 1022-13-5 1024-57-3, Heptachlor epoxide 1064-06-8, Quercetin pentaacetate 1072-53-3 1073-05-8 1120-71-4, 1,3-Propane sultone 1125-80-0, 3-Methylisoquinoline 1143-38-0, 1,8,9-Trihydroxyanthracene 1147-55-3 1162-65-8, Aflatoxin B1 1165-39-5, Aflatoxin G1 1239-45-8, Ethidium bromide 1421-85-8 1456-28-6 1464-53-5, 1,2:3,4-Diepoxybutane 1499-54-3 1563-66-2, Carbofuran 1582-09-8, Trifluralin 1594-56-5, 2,4-Dinitrophenyl thiocyanate 1606-67-3, 1-Aminopyrene 1633-83-6, 1,4-Butane sultone 1675-54-3 1694-09-3, Acid violet 6B 1792-40-1, 2-Methyl-5-nitrobenzimidazole 1838-56-8 1918-00-9 1934-21-0, Tartrazine 1936-15-8, Orange G 1951-56-0 1972-08-3 1982-49-6, Siduron 2270-40-8 2275-23-2, Vamidothion 2303-16-4, Diallate 2303-17-5, Triallate 2353-45-9, Fast green FCF 2381-15-9, 10-Methylbenz(a)anthracene 2381-31-9, 8-Methylbenz(a)anthracene 2381-40-0, 7,10-Dimethylbenz(c)acridine 2386-90-5 2417-77-8, 9-Bromomethylanthracene 2425-06-1, Captafol 2426-07-5, 1,2:7,8-Diepoxyoctane 2438-72-4 2465-27-2, Auramine 2481-94-9,

4-(Diethylamino)azobenzene 2491-52-3, 4-Nitroazobenzene 2508-20-5, 2-Nitrosofluorene 2541-69-7, 7-Methylbenz(a)anthracene 2578-75-8 2642-98-0, 6-Aminochrysene 2783-94-0, Sunset yellow FCF 2784-86-3 2788-86-5, p-Chlorostyrene oxide 2834-92-6, 1-Amino-2-naphthol 2921-88-2, Chlorpyriphos 2942-42-9, 7-Nitroindazole 3034-38-6, 4-Nitroimidazole 3034-42-2, 1-Methyl-5-nitroimidazole 3067-12-7, Benzo(a)pyrene-6,12-quinone 3067-13-8, Benzo(a)pyrene-1,6-quinone 3067-14-9, Benzo(a)pyrene-3,6-quinone 3105-97-3, Hycanthone 3118-97-6, Oil red XO 3244-90-4, Aspon 3308-64-3, 2-Hydroxy-3-methylcholanthrene 3342-98-1, 1-Hydroxy-3-methylcholanthrene 3343-07-5 3343-08-6, 3-Methylcholanthrene-2-one 3343-12-2 3544-23-8, 3-Methoxy-4-aminoazobenzene 3546-41-6, Pyrvinium pamoate 3564-09-8, Ponceau 3R 3567-69-9 3570-75-0 3688-53-7 3697-24-3, 5-Methylchrysene 3719-37-7 3719-40-2 3740-52-1, o-Nitrophenylacetic acid 3761-53-3 3778-73-2, Ifosfamide 3817-11-6 3844-45-9, Brilliant blue FCF 3923-52-2 4213-45-0, Quinacrine mustard 4245-76-5, 1-Methyl-3-nitroguanidine 4245-77-6 4426-50-0, 1,3-Butylene sulfate 4434-38-2 4548-53-2, Ponceau sx 4637-56-3 4803-27-4, Anthramycin 5036-03-3 5141-20-8 5208-87-7, 1'-Hydroxysafrole 5220-02-0 5275-69-4, 2-Acetyl-5-nitrofuran 5307-14-2, 2-Nitro-p-phenylenediamine 5336-53-8, Dibenzylnitrosamine 5401-94-5, 5-Nitroindazole 5461-85-8 5632-47-3, 1-Nitrosopiperazine 6098-44-8 6146-52-7, 5-Nitroindole 6236-05-1, Nifuroxime 6281-23-8, 5-Nitro-2-furylacrylic acid 6325-54-8 6332-56-5, 2-Hydroxy-3-nitropyridine

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (mutagenicity of, Computer Automated Structure Evaluation for study of structural determinants in relation to)

L22 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB Glutathione transferases were purified from 5 species of lepidopterous larvae using a 2-step procedure involving (NH4)2SO4 fractionation and affinity chromatog. on a glutathione-agarose column. The highly polyphagous insects, fall armyworm (Spodoptera frugiperda) and corn earworm (Heliothis zea), possessed multiple glutathione transferases contg. 6 and 4 isoenzymes, resp. On the other hand, the more specialized insects, **tobacco** budworm (Heliothis virescens), cabbage looper (Trichoplusia ni), and velvetbean caterpillar (Anticarsia gemmatalis), had a single form of the enzyme. These isoenzymes consisted of 2-4 subunits with mol. wts. of 27,000-32,000, depending on the species. Qual. differences in glutathione transferase isoenzymes were obsd. among these species based on their Km, isoelec. point, and relative mobility (electrophoresis). Induction of glutathione transferase in fall armyworm larvae by xanthotoxin increased levels of the existing isoenzymes but did not result in prodn. of any new isoenzyme.

ACCESSION NUMBER: 1990:3222 CAPLUS
DOCUMENT NUMBER: 112:3222
TITLE: Purification and characterization of glutathione transferases from five phytophagous Lepidoptera
AUTHOR(S): Yu, S. J.
CORPORATE SOURCE: Dep. Entomol. Nematol., Univ. Florida, Gainesville, FL, 32611, USA
SOURCE: Pestic. Biochem. Physiol. (**1989**), 35(1), 97-105
CODEN: PCBPBS; ISSN: 0048-3575
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Pestic. Biochem. Physiol. (**1989**), 35(1), 97-105
CODEN: PCBPBS; ISSN: 0048-3575

AB Glutathione transferases were purified from 5 species of lepidopterous larvae using a 2-step procedure involving (NH4)2SO4 fractionation and affinity chromatog. on a glutathione-agarose column. The highly polyphagous insects, fall armyworm (Spodoptera frugiperda) and corn earworm (Heliothis zea), possessed multiple glutathione transferases contg. 6 and 4 isoenzymes, resp. On the other hand, the more specialized insects, **tobacco** budworm (Heliothis virescens), cabbage looper (Trichoplusia ni), and velvetbean caterpillar (Anticarsia gemmatalis), had a single form of the enzyme. These isoenzymes consisted of 2-4 subunits with mol. wts. of 27,000-32,000, depending on the species. Qual. differences in glutathione transferase isoenzymes were obsd. among these species based on their Km, isoelec. point, and relative mobility (electrophoresis). Induction of glutathione transferase in fall armyworm larvae by xanthotoxin increased levels of the existing isoenzymes but did not result in prodn. of any new isoenzyme.

IT **298-81-7**, Xanthotoxin
RL: BIOL (Biological study)
(glutathione transferase isoenzymes induction by, in fall armyworm)

L22 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB Midgut microsomes prepd. from larvae of the fall armyworm (S. frugiperda), a generalist insect, and the velvetbean caterpillar (A. gemmatalis), a semispecialist, were used to study their oxidative activity toward a variety of allelochems. Allelochems. such as terpenoids, alkaloids, indoles, glucosinolates, flavonoids, coumarins, cardenolides, phenylpropenes, and a ketohydrocarbon were all metabolized by the microsomal cytochrome P 450 monooxygenases in both species. Fall armyworm microsomes oxidized monoterpenes more favorably than other types of terpenes, thus indicating a preference for these compds. In all instances, the oxidative metab. of these allelochems. could be induced by 1.3-9.5-fold by dietary allelochems. such as indole 3-carbinol, indole 3-acetonitrile, menthol, flavone, or peppermint oil. In the case of certain triterpenes, tetraterpenes, alkaloids, coumarin, and cardenolides, metabolic activity was only be obsd. after induction. The monooxygenase activities toward these allelochems. were generally higher in the generalist than in the semispecialist insect. Hence, microsomal monooxygenases play an important role in the detoxification of plant toxins and hence host-plant selections in herbivorous insects.

ACCESSION NUMBER: 1987:211276 CAPLUS
DOCUMENT NUMBER: 106:211276
TITLE: Microsomal oxidation of allelochemicals in generalist (Spodoptera frugiperda) and semispecialist (Anticarsia gemmatalis) insect
AUTHOR(S): Yu, S. J.
CORPORATE SOURCE: Dep. Entomol. Nematol., Univ. Florida, Gainesville, FL, 32611, USA
SOURCE: J. Chem. Ecol. (**1987**), 13(3), 423-36
CODEN: JCECD8; ISSN: 0098-0331
DOCUMENT TYPE: Journal
LANGUAGE: English

SO J. Chem. Ecol. (**1987**), 13(3), 423-36
CODEN: JCECD8; ISSN: 0098-0331

IT 51-55-8, Atropine, biological studies 54-11-5, **Nicotine** 57-24-9, Strychnine 57-87-4, Ergosterol 58-08-2, Caffeine, biological studies 71-63-6, Digitoxin 83-46-5 83-48-7, Stigmasterol 83-79-4, Rotenone 89-82-7, (+)-Pulegone 91-64-5, Coumarin 92-61-5, Scopoletin 94-59-7, Safrole 111-02-4, Squalene 120-58-1, Isosafrole **298-81-7**, Xanthotoxin 315-22-0, Monocrotaline 525-82-6,

Flavone 607-91-0, Myristicin 1672-46-4, Digoxigenin 2257-09-2, 2-Phenylethyl isothiocyanate 2591-98-2, Indole 3-acetaldehyde 3952-98-5, Sinigrin 7235-40-7, .beta.-Carotene
RL: RCT (Reactant)
(oxidn. of, by midgut microsomes of fall armyworm)

L22 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2002 ACS
AB The induction of sister chromatid exchanges (SCE) and mutation at the hypoxanthine-guanine phosphoribosyl transferase locus and toxicities of 40 different chem. and phys. agents were examd. on Chinese hamster V-79 cells. Mutation was measured as resistance to 6-thioguanine [154-42-7] and toxicity as loss of cell plating efficiency. SCE were examd. 29 h after treatment. With the agents examd., a highly pos. correlation existed between SCE-inducing and mutagenic potencies, when expressed as the increase in the no. per a unit dose over the control values. But the great difference of the ratios of mutagenic potencies vs. SCE-inducing potencies among agents was obsd., the max. difference being .apprx.200-fold. The agents that showed the higher values of the ratio (agents producing more mutations than SCE) were bleomycin [11056-06-7], Co-60 .gamma.-rays, all the ethylating agents (N-ethyl-N-nitrosourea [759-73-9], N-ethyl-N'-nitro-N-nitrosoguanidine [4245-77-6], Et methanesulfonate [62-50-0], and di-Et sulfate [64-67-5]), N-propyl-N-nitrosourea [816-57-9], N-butyl-N-nitrosourea [869-01-2], isoPr methanesulfonate [926-06-7], intercalating acridine compds. [2-methoxy-6-chloro-9-[3-(ethyl-2-chloroethylamino)propylamino]acridine-2HCl [146-59-8] and 2-methoxy-6-chloro-9-[3-(chloroethylamino)propylamino]acridine-2HCl [17070-45-0]], and UV light at 254 nm. The agents that showed the lower values (agents producing more SCE than mutations) were Pt compds. (cis-diamminedichloroplatinum [15663-27-1] and trans-diamminedichloroplatinum [14913-33-8]), epoxides (epichlorohydrin [106-89-8], styrene oxide [96-09-3], and diepoxybutane [1464-53-5]) and aziridines [mitomycin C [50-07-7], decarbamoyl mitomycin C [26909-37-5], tris(1-aziridinyl)phosphine sulfide [52-24-4], triethylenemelamine [51-18-3], and carboquone [24279-91-2]]. The agents showed the intermediate values included all methylating agents (N-methyl-N-nitosourea [684-93-5], N-methyl-N'-nitro-N-nitrosoguanidine [70-25-7], Me methanesulfonate [66-27-3], and di-Me sulfate [77-78-1]), N-(2-hydroxyethyl)ethyleneimine [1072-52-2], .beta.-propiolactone [57-57-8], treatment of 8-methoxypsoralen [**298-81-7**] plus near-UV light irradn. at 352 nm, 4-nitroquinoline 1-oxide [56-57-5], quinacrine mustard [4213-45-0], sodium sorbate [7757-81-5], cigarette tar, and diesel tar. For most agents that induced SCE, the toxicity dependency of induced SCE was rather biphasic; increase in SCE was steep at low to moderate toxicity and less at moderate to high toxicity. At equitoxic doses, the agents showed great difference in induction of SCE.

ACCESSION NUMBER: 1984:505581 CAPLUS
DOCUMENT NUMBER: 101:105581
TITLE: Comparison of 6-thioguanine-resistant mutation and sister chromatid exchanges in Chinese hamster V-79 cells with forty chemical and physical agents
AUTHOR(S): Nishi, Yoshisuke; Hasegawa, Makiko M.; Taketomi, Masako; Ohkawa, Yoshihiko; Inui, Naomichi
CORPORATE SOURCE: Biol. Res. Cent., Japan Tob. and Salt Publ. Corp., Kanagawa, 257, Japan
SOURCE: Cancer Res. (**1984**), 44(8), 3270-9
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Cancer Res. (**1984**), 44(8), 3270-9
CODEN: CNREA8; ISSN: 0008-5472

AB The induction of sister chromatid exchanges (SCE) and mutation at the hypoxanthine-guanine phosphoribosyl transferase locus and toxicities of 40 different chem. and phys. agents were examd. on Chinese hamster V-79 cells. Mutation was measured as resistance to 6-thioguanine [154-42-7] and toxicity as loss of cell plating efficiency. SCE were examd. 29 h after treatment. With the agents examd., a highly pos. correlation existed between SCE-inducing and mutagenic potencies, when expressed as the increase in the no. per a unit dose over the control values. But the great difference of the ratios of mutagenic potencies vs. SCE-inducing potencies among agents was obsd., the max. difference being .apprx.200-fold. The agents that showed the higher values of the ratio (agents producing more mutations than SCE) were bleomycin [11056-06-7], Co-60 .gamma.-rays, all the ethylating agents (N-ethyl-N-nitrosourea [759-73-9], N-ethyl-N'-nitro-N-nitrosoguanidine [4245-77-6], Et methanesulfonate [62-50-0], and di-Et sulfate [64-67-5]), N-propyl-N-nitrosourea [816-57-9], N-butyl-N-nitrosourea [869-01-2], isoPr methanesulfonate [926-06-7], intercalating acridine compds. [2-methoxy-6-chloro-9-[3-(ethyl-2-chloroethylamino)propylamino]acridine-2HCl [146-59-8] and 2-methoxy-6-chloro-9-[3-(chloroethylamino)propylamino]acridine-2HCl [17070-45-0]], and UV light at 254 nm. The agents that showed the lower values (agents producing more SCE than mutations) were Pt compds. (cis-diamminedichloroplatinum [15663-27-1] and trans-diamminedichloroplatinum [14913-33-8]), epoxides (epichlorohydrin [106-89-8], styrene oxide [96-09-3], and diepoxybutane [1464-53-5]) and aziridines [mitomycin C [50-07-7], decarbamoyl mitomycin C [26909-37-5], tris(1-aziridinyl)phosphine sulfide [52-24-4], triethylenemelamine [51-18-3], and carboquone [24279-91-2]]. The agents showed the intermediate values included all methylating agents (N-methyl-N-nitosourea [684-93-5], N-methyl-N'-nitro-N-nitrosoguanidine [70-25-7], Me methanesulfonate [66-27-3], and di-Me sulfate [77-78-1]), N-(2-hydroxyethyl)ethyleneimine [1072-52-2], .beta.-propiolactone [57-57-8], treatment of 8-methoxypsoralen [**298-81-7**] plus near-UV light irradn. at 352 nm, 4-nitroquinoline 1-oxide [56-57-5], quinacrine mustard [4213-45-0], sodium sorbate [7757-81-5], cigarette tar, and diesel tar. For most agents that induced SCE, the toxicity dependency of induced SCE was rather biphasic; increase in SCE was steep at low to moderate toxicity and less at moderate to high toxicity. At equitoxic doses, the agents showed great difference in induction of SCE.

IT **Tobacco** smoke and **smoking**
(tar, sister chromatid exchange and cell thioguanine-resistant mutation from, in V-79 cells, comparison of)

IT 50-07-7 51-18-3 52-24-4 55-86-7 56-57-5 57-57-8 62-50-0 64-67-5 66-27-3 70-25-7 77-78-1 96-09-3 106-89-8, biological studies 134-50-9 146-59-8 **298-81-7** 553-30-0 684-93-5 759-73-9 816-57-9 869-01-2 926-06-7 1072-52-2 1239-45-8 1464-53-5 4213-45-0 4245-77-6 7722-84-1, biological studies 7757-81-5 11056-06-7 14913-33-8 15663-27-1 17070-45-0 24279-91-2 26909-37-5 75142-42-6
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(sister chromatid exchange and thioguanine-resistant mutation from, in V-79 cells, comparison of)

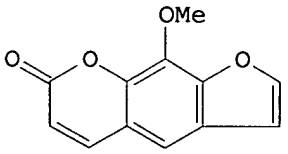
L22 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB A method for sepg. nonpolar mutagens from their dil. aq. solns. is described. It utilizes the affinity of the mutagens to a phthalocyanine

deriv. attached to cotton through a covalent bond. For mutagens having .gtoreq.3 fused arom. rings in their structures, efficient adsorption took place on soaking the cotton in their solns. The mutagens adsorbed can be recovered by elution with ammoniacal MeOH. Mutagenicity in smoker's urine, cooked beef, and river water was detected by use of this method.

ACCESSION NUMBER: 1983:174206 CAPLUS
DOCUMENT NUMBER: 98:174206
TITLE: Adsorption of mutagens to cotton bearing covalently bound trisulfo-copper-phthalocyanine
AUTHOR(S): Hayatsu, Hikoya; Oka, Takanori; Wakata, Akihiro; Ohara, Yoshiko; Hayatsu, Toshiko; Kobayashi, Hiroshi; Arimoto, Sakae
CORPORATE SOURCE: Fac. Pharm. Sci., Okayama Univ., Tsushima, 700, Japan
SOURCE: Mutat. Res. (**1983**), 119(3-4), 233-8
CODEN: MUREAV; ISSN: 0027-5107
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Mutat. Res. (**1983**), 119(3-4), 233-8
CODEN: MUREAV; ISSN: 0027-5107
IT Urine analysis
(mutagens detection in, of **tobacco smoking** humans, copper phthalocyanine deriv. bound to cotton in)
IT **Tobacco** smoke and **smoking**
(urine of humans after, mutagens detection in, copper phthalocyanine deriv. bound to cotton in)
IT 50-32-8, biological studies 50-53-3, biological studies 53-96-3 56-57-5 62-75-9 71-00-1, biological studies 73-22-3, biological studies 73-24-5, biological studies 83-89-6 90-45-9 99-56-9 100-02-7, biological studies 112-80-1, biological studies 153-78-6 244-63-3 **298-81-7** 613-13-8 1239-45-8 2423-66-7 3688-53-7 5522-43-0 6804-07-5 20830-81-3 26148-68-5 62450-06-0 62450-07-1 67730-10-3 67730-11-4 68006-83-7 76180-96-6 77500-04-0 83584-84-3
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(adsorption of, to copper phthalocyanine deriv. bound on cotton, sepn. in relation to)

L22 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2002 ACS
GI



I

AB Four different psoralens were tested for their photobiochem. effect on TMV (**tobacco** mosaic virus)-RNA messenger activity. 8-Methoxypsoralen (8-MOP)(I) [**298-81-7**] and 4,5',8-trimethylpsoralen (TMP) [3902-71-4] were able to cause partial loss of template activity, whereas 4'-hydroxymethyl-4,5',8-trimethylpsoralen (HMT) [62442-59-5] and 4'-aminomethyl-4,5',8-trimethylpsoralen (AMT) [64358-50-5] caused total irreversible loss of activity. When used at submaximal concns., HMT, AMT, and TMP caused a selective inhibition of the synthesis of polypeptides of high mol. wt.

8-MOP did not show such a preferential inhibitory effect.

ACCESSION NUMBER: 1981:508461 CAPLUS
DOCUMENT NUMBER: 95:108461
TITLE: Photochemical effect of psoralens on TMV-RNA messenger activity in in vitro protein synthesis
AUTHOR(S): Leick, Vagn; Nielsen, Peter E.
CORPORATE SOURCE: Biochem. Inst. B, Univ. Copenhagen, Copenhagen, DK-2200, Den.
SOURCE: Photobiochem. Photobiophys. (**1981**), 2(4-5), 285-90
CODEN: PHOPDS; ISSN: 0165-8646
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Photobiochem. Photobiophys. (**1981**), 2(4-5), 285-90
CODEN: PHOPDS; ISSN: 0165-8646
AB Four different psoralens were tested for their photobiochem. effect on TMV (**tobacco** mosaic virus)-RNA messenger activity. 8-Methoxypsoralen (8-MOP)(I) [**298-81-7**] and 4,5',8-trimethylpsoralen (TMP) [3902-71-4] were able to cause partial loss of template activity, whereas 4'-hydroxymethyl-4,5',8-trimethylpsoralen (HMT) [62442-59-5] and 4'-aminomethyl-4,5',8-trimethylpsoralen (AMT) [64358-50-5] caused total irreversible loss of activity. When used at submaximal concns., HMT, AMT, and TMP caused a selective inhibition of the synthesis of polypeptides of high mol. wt. 8-MOP did not show such a preferential inhibitory effect.
IT **298-81-7** 3902-71-4 62442-59-5 64358-50-5
RL: BIOL (Biological study)
(photochem. activity of and protein synthesis response to)

L22 ANSWER 18 OF 19 USPATFULL
AB The present invention concerns a transdermal system with a reservoir layer comprising an active substance, at least part of which is in the form of an inclusion complex formed between a cyclo compound and the active substance. The release rate from the system is controlled by the dissociation of the complex.

ACCESSION NUMBER: 92:46878 USPATFULL
TITLE: Transdermal system
INVENTOR(S): Hansen, Jens, Allerod, Denmark
Mollgaard, Birgitte, Virum, Denmark
PATENT ASSIGNEE(S): Pharmacia AB, Sweden (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5120546		19920609	<--
APPLICATION INFO.:	US 1990-490088		19900307	(7)

	NUMBER	DATE
PRIORITY INFORMATION:	SE 1989-4296	19891221

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Page, Thurman K.
ASSISTANT EXAMINER: Phelan, D. Gabrielle
LEGAL REPRESENTATIVE: Pravel, Gambrell, Hewitt, Kimball & Krieger
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 3 Drawing Page(s)

LINE COUNT: 862
PI US 5120546 19920609 <--
DRWD FIG. 4 is a graphic depiction of the release of **nicotine** from the transdermal drug delivery system of example 7; systems 6 and 7.
DRWD FIG. 5 is a graphic depiction of permeation of **nicotine** through human epidermis from the transdermal drug delivery system of example 10; system 8.
DETD . . . agents (e.g. heparin, warfarin), diuretics (e.g. hydrochlorothiazide, flunarizine, minoxidil), antihypertensive agents (e.g. propanolol, metoprolol, clonidine, pindolol), chemical dependency drugs (e.g. **nicotine**, methandone), local anaesthetics (e.g. lidocaine, prilocaine, benzocaine), corticosteroids (e.g. beclomethasone, betamethasone, clobetasol, desonide, desoxymethasone, dexamethasone, diflucortolone, flumethasone, fluocinolone acetonide, fluocinonide, hydrocortisone, methylprednisolon, triamcinolone acetonide, budesonide, halcinonide), dermatological agents (e.g. nitrofurantoin, dithranol, clioquinol, hydroxyquinoline, isotretinoin, **methoxsalen**, methotrexate, tretinoin, trioxsalen, salicylic acid, penicillamine), and the like.
DETD . . . a nitro compound such as amyl nitrates, nitroglycerine and isosorbide nitrates; an amine compound such as prilocaine, oxybutyninchloride, lidocaine, benzocaine, **nicotine**, chlorpheniramine, terfenadine, triprolidine, propanolol and metoprolol; an oxicam derivative such as piroxicam; a mucopolysaccharide such as thiomucase; an opioid such. . .
DETD Cinnamyl alcohol, Zimtalkohol zur Synthese, Merck-Schuchardt: Cinnamyl alcohol is used as a model substance. **Nicotine**, (-)-Nicotin zur Synthese, Merck-Schuchardt Polyvidon 90, polyvinyl pyrrolidone, BASF Propylene glycol, Ph. Eur. 2nd Ed.
DETD .beta.-cyclodextrin inclusion complexes of cinnamyl alcohol (.beta.-CD-CA) and **nicotine** (.beta.-CD-N) were prepared in our laboratory.
DETD Preparation of inclusion complex of .beta.-CD and **nicotine** (.beta.-CD-N).
DETD . . . were heated to 75.degree. C. 28 g of .beta.-CD were added and dissolved while stirring the solution. 3.5 ml of **nicotine** were added. The mixture was stirred for about 4 h at ambient temperature. The obtained mixture was filtered and dried. . .
DETD Transdermal drug delivery system with **nicotine** as the active substance.
DETD The resulting sheet with backing layer, reservoir layer and adhesive layer was 119 .mu.m thick. The concentration of **nicotine** was determined according to example 8 to 0.4 mg **nicotine** per cm.sup.2.
DETD 1000 .mu.l **nicotine** and 400 .mu.l propylene glycol were added to 12.6 g polyvidon 90 gel (example 3) to give the drug gel.. . .
DETD The resulting sheet with backing layer, reservoir layer and adhesive layer was 109 .mu.m thick. The concentration of **nicotine** was determined according to example 8 to 0.2 mg **nicotine** per cm.sup.2.
DETD . . . The results of those studies are reported graphically in FIG. 4. From system 6 which comprises .beta.-cyclodextrin inclusion complex of **nicotine** in the reservoir layer **nicotine** is released with a slower rate than from system 7 which comprises neat **nicotine** without .beta.-cyclodextrin in the reservoir layer. As shown, the release rate of **nicotine** from system 6 declined slightly over the period but more closely approximated zero order release than first order release.

DETD . . . extracted with 5.00 ml ethanol in the case of cinnamyl alcohol, and 5.00 ml 0.01N HCl in the case of **nicotine**. The extracted amount of active substance was determined by UV-spectrophotometry (.lambda.max. (cinnamyl alcohol)=251 nm, .lambda.max. (**nicotine**)=260 nm), and the concentration of the systems was expressed in mg active substance per cm.sup.2.

DETD . . . periodically and measuring the concentration of the drugs. The receptor phase was 15.00 ml 0.01N HCl in the studies with **nicotine** and 15.00 ml phosphate buffer 0.05M pH 7.4 in the studies with cinnamyl alcohol.

DETD In vitro permeation from transdermal drug delivery system with **nicotine** as the active substance.

DETD The resulting sheet with backing layer, reservoir layer and adhesive layer was 0.5 mm thick and the concentration of **nicotine** was determined according to example 8 to 1.4 mg cm.sup.-2.

DETD In vitro permeation of **nicotine** from transdermal system 8 across human epidermis was investigated with Franz diffusion cells.

DETD Permeation of **nicotine** was followed by removing samples periodically and measuring the concentration by a HPLC method according to example 11. The cumulative amount of **nicotine** appearing in the recipient phase versus time are shown in FIG. 5. As it appears, system 8 revealed approximately zero order permeation kinetics although the permeation rate of **nicotine** declined slightly over the period. The initial permeation rate was calculated to 22.2 .mu.g cm.sup.-2 h.sup.-1.

DETD Quantitative determination of **nicotine** content in the recipient phase samples from skin permeation studies was done by a HPLC method. A LKB system comprising. . .

CLM What is claimed is:

. . . the active substance is selected from the group consisting of steroids, amyl nitrates, nitroglycerine, isosorbide nitrates, prilocaine, oxybutyninchloride, lidocaine, benzocaine, **nicotine**, chlorpheniramine, terfenadine, triprolidinee, propanol, metroprolol, oxicam derivatives, opioids, prostaglandines, benzamides, peptides, xanthines, catecholamines, dihydropyridines, thiazides, sulfated polysaccarides and mucopolysaccaraides.

8. A transdermal system according to claim 7, wherein the drug is **nicotine**.

13. The method of claim 11, wherein the active substance is **nicotine**.

L22 ANSWER 19 OF 19 USPATFULL

AB Silica gel is treated with a reactive phthalocyanine compound to form the blue silica gel, which has a phthalocyanine skeleton linked through an organic group. Typically, a phthalocyanine reactive dye is used for the reaction with silica gel at its hydroxyl or other reactive site. The blue silica gel easily adsorbs and desorbs the polycyclic organic substances in a solution. The blue silica gel can be used for the separation or removal of the mutagenic substances from the environment, foodstuffs, etc.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 86:64931 USPATFULL

TITLE: Silica gel linked to a phthalocyanine compound and a method for treating polycyclic organic substances

therewith

INVENTOR(S): Hayatsu, Hikoya, Okayama, Japan
Nakano, Masahide, Hirakata, Japan
Matsuo, Yoshikazu, Sakai, Japan

PATENT ASSIGNEE(S): Sumitomo Chemical Company, Limited, Osaka, Japan
(non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 4623638		19861118	<--
APPLICATION INFO.:	US 1985-714675		19850321	(6)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1984-60262	19840327

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Garvin, Patrick P.
LEGAL REPRESENTATIVE: Cushman, Darby & Cushman
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
LINE COUNT: 289
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 4623638 19861118 <--

SUMM . . . in the selective adsorption, desorption, concentration and separation, of polycyclic organic substances, such as those present in the environment, foodstuffs, **tobacco**, living body samples, etc. in extremely small quantities. For instance, the method of the present invention can be applied for. . . the mutagenic substances from beef extract, quantification of the mutagenic substances in urine, and removal of the mutagenic substances in **tobacco** smoke and exhaust gas.

IT 50-53-3, analysis 53-96-3 73-22-3, analysis 73-24-5, analysis
83-89-6 90-45-9 153-78-6 244-63-3 **298-81-7** 1239-45-8
26148-68-5 62450-06-0 67730-10-3 67730-11-4 68006-83-7
76180-96-6 77500-04-0 100822-01-3
(sepn. of, phthalocyanine-contg. silica gel stationary phase in HPLC)

=>

L4 ANSWER 8 OF 64 CAPLUS COPYRIGHT 2002 ACS

AB The title method using psycho- and reflexotherapy was proposed. With the purpose of enhancing of efficiency of therapy 5-6 h before the start of the reflexotherapeutic procedure oral cavity was irrigated by 1.0% soln. of pilocarpine hydrochloride and Et chloride with simultaneous inhalation of Et chloride vapors.

ACCESSION NUMBER: 1994:238085 CAPLUS
DOCUMENT NUMBER: 120:238085
TITLE: Method of abstinence syndrome treatment in tobacco dependence
INVENTOR(S): Garnitskij, Sergej P.; Shuteeva, Larisa V.
PATENT ASSIGNEE(S): "Know How" Cooperative Medical Center, USSR
SOURCE: U.S.S.R. From: Izobreteniya 1993, (11), 11.
CODEN: URXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Russian
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
	SU 1803032	A1	19930323	SU 1990-4859314	19900322	<--
PI	SU 1803032 A1 **19930323**					
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	SU 1803032	A1	19930323	SU 1990-4859314	19900322	<--

ST **tobacco dependence** abstinence syndrome reflexotherapy psychotherapy; **pilocarpine** hydrochloride **tobacco dependence** abstinence syndrome; Et chloride **tobacco dependence** abstinence syndrome

IT 54-71-7, **Pilocarpine** hydrochloride 75-00-3, Ethyl chloride
RL: BIOL (Biological study)
(in **tobacco dependence** abstinence syndrome treatment)

=>

→ administer pilocarpine HCL 1% soln to the tongue (of humans)
→ quantity 0.2-0.5 ml over course of 1-2 seconds
→

=> s cyp2b6(p)(inhibitor or antagonsit#) and (nicotine or cyp2a6 or cotinine or tobacco or smoking)
L14 22 CYP2B6(P)(INHIBITOR OR ANTAGONSIT#) AND (NICOTINE OR CYP2A6 OR COTININE OR TOBACCO OR SMOKING)

=> s l14 and py <=1999
L15 19 L14 AND PY <=1999

=> d l15 abs ibib kwic 1-19

L15 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2002 ACS
AB N-Nitrosobenzylmethylamine (NBzMA) is a potent esophageal carcinogen in rodents, and has been found as a dietary contaminant in certain areas of China where esophageal cancer is endemic. To det. which cytochrome P 450 enzymes in humans are primarily responsible for NBzMA metab., microsomes from lymphoblastoid cell lines expressing a panel of human cytochrome P-450s (CYP1A1, CYP1A2, **CYP2A6**, **CYP2B6**, CYP2D6, CYP2E1, CYP2C9, CYP2C19, and CYP3A4) and a panel of 10 different human liver microsomal prepns. were examd. for their abilities to metabolize [3H]NBzMA. In addn., the ability of human liver microsomes to form various NBzMA metabolites was correlated with the abilities of these prepns. to metabolize coumarin, ethoxyresorufin, chlorzoxazone, 7-ethoxy-4-trifluoromethylcoumarin, S-mephenytoin, and nifedipine. NBzMA metabolites were quantitated by reversed-phase high-performance liq. chromatog. (HPLC) coupled with flow-through radioactivity detection. Major metabolites included benzaldehyde, benzyl alc., benzoic acid, and several uncharacterized radioactive peaks. Of the representative P 450 activities, only CYP2E1 and **CYP2A6** catalyzed substantial metab. of NBzMA. Compared to CYP2E1, **CYP2A6** metabolized NBzMA more readily. NBzMA acted as a potent **inhibitor** of coumarin 7-hydroxylation in **CYP2A6** microsomes. Human liver microsomes metabolized NBzMA readily. NBzMA metabolite formation was most highly correlated with coumarin 7-hydroxylase activity, a marker of **CYP2A6** activity. 8-Methoxypsoralen substantially inhibited NBzMA metab. in human hepatic microsomes. When the effects of the potent isothiocyanates PEITC and PHITC were analyzed on microsomes from cell lines expressing CYP2E1 and **CYP2A6**, it was found that PEITC inhibited both enzymes, PHITC was the more effective **inhibitor** of CYP2E1, and PHITC was an ineffective **inhibitor** of **CYP2A6**. Collectively, these data indicate that **CYP2A6** and, to a lesser degree, CYP2E1 are important P 450 enzymes in the activation of NBzMA in human systems.

ACCESSION NUMBER: 1999:779961 CAPLUS
DOCUMENT NUMBER: 132:103991
TITLE: Metabolism of N-nitrosobenzylmethylamine by human cytochrome P-450 enzymes
AUTHOR(S): Morse, Mark A.; Lu, Jerry; Stoner, Gary D.; Murphy, Sharon E.; Peterson, Lisa A.
CORPORATE SOURCE: Division of Environmental Health Sciences, Ohio State University School of Public Health, Columbus, OH, USA
SOURCE: Journal of Toxicology and Environmental Health, Part A (1999), 58(7), 397-411
CODEN: JTEHF8
PUBLISHER: Taylor & Francis
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Journal of Toxicology and Environmental Health, Part A (1999), 58(7), 397-411
CODEN: JTEHF8

AB N-Nitrosobenzylmethylamine (NBzMA) is a potent esophageal carcinogen in rodents, and has been found as a dietary contaminant in certain areas of China where esophageal cancer is endemic. To det. which cytochrome P 450 enzymes in humans are primarily responsible for NBzMA metab., microsomes from lymphoblastoid cell lines expressing a panel of human cytochrome P-450s (CYP1A1, CYP1A2, **CYP2A6**, **CYP2B6**, CYP2D6, CYP2E1, CYP2C9, CYP2C19, and CYP3A4) and a panel of 10 different human liver microsomal prepns. were examd. for their abilities to metabolize [3H]NBzMA. In addn., the ability of human liver microsomes to form various NBzMA metabolites was correlated with the abilities of these prepns. to metabolize coumarin, ethoxyresorufin, chlorzoxazone, 7-ethoxy-4-trifluoromethylcoumarin, S-mephenytoin, and nifedipine. NBzMA metabolites were quantitated by reversed-phase high-performance liq. chromatog. (HPLC) coupled with flow-through radioactivity detection. Major metabolites included benzaldehyde, benzyl alc., benzoic acid, and several uncharacterized radioactive peaks. Of the representative P 450 activities, only CYP2E1 and **CYP2A6** catalyzed substantial metab. of NBzMA. Compared to CYP2E1, **CYP2A6** metabolized NBzMA more readily. NBzMA acted as a potent **inhibitor** of coumarin 7-hydroxylation in **CYP2A6** microsomes. Human liver microsomes metabolized NBzMA readily. NBzMA metabolite formation was most highly correlated with coumarin 7-hydroxylase activity, a marker of **CYP2A6** activity. 8-Methoxypsoralen substantially inhibited NBzMA metab. in human hepatic microsomes. When the effects of the potent isothiocyanates PEITC and PHITC were analyzed on microsomes from cell lines expressing CYP2E1 and **CYP2A6**, it was found that PEITC inhibited both enzymes, PHITC was the more effective **inhibitor** of CYP2E1, and PHITC was an ineffective **inhibitor** of **CYP2A6**. Collectively, these data indicate that **CYP2A6** and, to a lesser degree, CYP2E1 are important P 450 enzymes in the activation of NBzMA in human systems.

L15 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB The role of cytochrome P-450s (CYPs) in S-mephobarbital N-demethylation was investigated by using human liver microsomes and cDNA-expressed CYPs. Among the 10 cDNA-expressed CYPs studied (CYP1A1, CYP1A2, **CYP2A6**, **CYP2B6**, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4), only **CYP2B6** could catalyze S-mephobarbital N-demethylation. The apparent Km values of human liver microsomes for S-mephobarbital N-demethylation were close to that of cDNA-expressed **CYP2B6** (about 250 .mu.M). The N-demethylase activity of S-mephobarbital in 10 human liver microsomes was strongly correlated with immunodetectable **CYP2B6** levels ($r = 0.920$, $p < .001$). Orphenadrine (300 .mu.M), a **CYP2B6 inhibitor**, inhibited the N-demethylase activity of S-mephobarbital in human liver microsomes to 29% of control activity. Therefore, it appears that **CYP2B6** mainly catalyzes S-mephobarbital N-demethylation in human liver microsomes.

ACCESSION NUMBER: 1999:778686 CAPLUS
DOCUMENT NUMBER: 132:87725
TITLE: Role of human CYP2B6 in S-mephobarbital N-demethylation
AUTHOR(S): Kobayashi, Kaoru; Abe, Seiji; Nakajima, Miki; Shimada, Noriaki; Tani, Masayoshi; Chiba, Kan; Yamamoto, Toshinori

CORPORATE SOURCE: Department of Clinicl Pharmacy, School of Pharmaceutical Sciences, Showa University, Tokyo, Japan
SOURCE: Drug Metabolism and Disposition (1999), 27(12), 1429-1433
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Drug Metabolism and Disposition (**1999**), 27(12), 1429-1433
CODEN: DMDSAI; ISSN: 0090-9556

AB The role of cytochrome P-450s (CYPs) in S-mephobarbital N-demethylation was investigated by using human liver microsomes and cDNA-expressed CYPs. Among the 10 cDNA-expressed CYPs studied (CYP1A1, CYP1A2, **CYP2A6**, **CYP2B6**, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4), only **CYP2B6** could catalyze S-mephobarbital N-demethylation. The apparent Km values of human liver microsomes for S-mephobarbital N-demethylation were close to that of cDNA-expressed **CYP2B6** (about 250 .mu.M). The N-demethylase activity of S-mephobarbital in 10 human liver microsomes was strongly correlated with immunodetectable **CYP2B6** levels ($r = 0.920$, $p < .001$). Orphenadrine (300 .mu.M), a **CYP2B6 inhibitor**, inhibited the N-demethylase activity of S-mephobarbital in human liver microsomes to 29% of control activity. Therefore, it appears that **CYP2B6** mainly catalyzes S-mephobarbital N-demethylation in human liver microsomes.

L15 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB Cytochrome P 450 (CYP) 3A4 is an inordinately important CYP enzyme that catalyzes the metab. of a vast array of clin. used drugs. Microsomal proteins of Spodoptera frugiperda (Sf21) insect cells infected with recombinant baculoviruses encoding CYP3A4 cDNA were used to immunize mice and to develop a monoclonal antibody (mAb3A4a) specific to CYP3A4 through the use of hybridoma technol. The mAb is both a potent **inhibitor** and a strong binder of CYP3A4. One and 5 .mu.l (0.5 and 2.5 .mu.M IgG2a) of the mAb mouse ascites in 1-mL incubation contg. 20 pmol of CYP3A4 strongly inhibited the testosterone 6.beta.-hydroxylation by 95 and 99%, resp., and, to a lesser extent, cross-inhibited CYP3A5 and CYP3A7 activity. MAb3A4a exhibited no cross-reactivity with any of the other recombinant human CYP isoforms (CYP1A1, CYP1A2, **CYP2A6**, **CYP2B6**, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1) in the course of CYP reaction phenotyping and Western immunoblot analyses. The potency of mAb-induced inhibition is insensitive to substrate concn. in human liver microsomes. Therefore, mAb3A4a was used to assess the quant. role of CYP3A4/5 to the metab. of testosterone and diazepam in five human liver microsomes. The results showed that CYP3A4 and CYP3A5 contribute >95% to both testosterone 6.beta.-hydroxylation and diazepam 3-hydroxylation and 52 to 73% to diazepam N-demethylation, resp. In addn., mAb3A4a significantly inhibited testosterone 6.beta.-hydroxylase activity in rhesus monkey liver microsomes to a degree equal to that obsd. with CYP3A4 in human liver microsomes. By comparison, no inhibition of testosterone 6.beta.-hydroxylase activity was obsd. in the presence of dog, rat, and mouse liver microsomes. The selectivity of ketoconazole, a chem. **inhibitor** of CYP3A4, was probed with mAb3A4a and was shown to be highly concn. dependent in the diazepam N-demethylation by human liver microsomes. The results demonstrate that inhibitory and immunoblotting

mAb3A4a can offer a precise and useful tool for quant. identification of CYP3A4/5 in the metab. of drugs in clin. use and drugs in development.

ACCESSION NUMBER: 1999:714281 CAPLUS
DOCUMENT NUMBER: 132:30280
TITLE: Role of a potent inhibitory monoclonal antibody to cytochrome P-450 3A4 in assessment of human drug metabolism
AUTHOR(S): Mei, Qin; Tang, Cuyue; Assang, Carol; Lin, Yuh; Slaughter, Donald; Rodrigues, A. David; Baillie, Thomas A.; Rushmore, Thomas H.; Shou, Magang
CORPORATE SOURCE: Department of Drug Metabolism, Merck Research Laboratories, West Point, PA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**1999**), 291(2), 749-759
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Journal of Pharmacology and Experimental Therapeutics (**1999**), 291(2), 749-759
CODEN: JPETAB; ISSN: 0022-3565

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L15 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB Aims: The study aimed to identify the specific human cytochrome P 450 (CYP450) enzymes involved in the metab. of artemisinin. Methods:

Microsomes from human B-lymphoblastoid cell lines transformed with individual CYP450 cDNAs were investigated for their capacity to metabolize artemisinin. The effect on artemisinin metab. in human liver microsomes by chem. inhibitors selective for individual forms of CYP450 was investigated. The relative contribution of individual CYP450 isoenzymes to artemisinin metab. in human liver microsomes was evaluated with a tree-based regression model of artemisinin disappearance rate and specific CYP450 activities. Results: The involvement of **CYP2B6** in artemisinin metab. was demonstrated by metab. of artemisinin by recombinant **CYP2B6**, inhibition of artemisinin disappearance in human liver microsomes by orphenadrine (76%) and primary inclusion of **CYP2B6** in the tree-based regression model. Recombinant CYP3A4 was catalytically competent in metabolizing artemisinin, although the rate was 10% of that for recombinant **CYP2B6**. The tree-based regression model suggested CYP3A4 to be of importance in individuals with low **CYP2B6** expression. Even though ketoconazole inhibited artemisinin metab. in human liver microsomes by 46%, incubation with ketoconazole together with orphenadrine did not increase the inhibition of artemisinin metab. compared to orphenadrine alone. Troleandomycin failed to inhibit artemisinin metab. The rate of artemisinin metab. in recombinant **CYP2A6** was 15% of that for recombinant **CYP2B6**. The inhibition of artemisinin metab. in human liver microsomes by 8-methoxypsoralen (a **CYP2A6 inhibitor**) was 82% but **CYP2A6** activity was not included in the regression tree. Conclusions: Artemisinin metab. in human liver microsomes is mediated primarily by **CYP2B6** with probable secondary contribution of CYP3A4 in individuals with low **CYP2B6** expression. The contribution of **CYP2A6** to artemisinin metab. is likely of minor importance.

ACCESSION NUMBER: 1999:692699 CAPLUS
DOCUMENT NUMBER: 132:175297
TITLE: Identification of the human cytochrome P450 enzymes involved in the in vitro metabolism of artemisinin
AUTHOR(S): Svensson, U. S. H.; Ashton, M.
CORPORATE SOURCE: Department of Pharmacy, Division of Biopharmaceutics and Pharmacokinetics, Uppsala University, Uppsala, S-751 23, Swed.
SOURCE: British Journal of Clinical Pharmacology (**1999**), 48(4), 528-535
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO British Journal of Clinical Pharmacology (**1999**), 48(4), 528-535
CODEN: BCPHBM; ISSN: 0306-5251

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recombinant **CYP2B6**, inhibition of artemisinin disappearance in human liver microsomes by orphenadrine (76%) and primary inclusion of **CYP2B6** in the tree-based regression model. Recombinant CYP3A4 was catalytically competent in metabolizing artemisinin, although the rate was 10% of that for recombinant **CYP2B6**. The tree-based regression model suggested CYP3A4 to be of importance in individuals with low **CYP2B6** expression. Even though ketoconazole inhibited artemisinin metab. in human liver microsomes by 46%, incubation with ketoconazole together with orphenadrine did not increase the inhibition of artemisinin metab. compared to orphenadrine alone. Troleandomycin failed to inhibit artemisinin metab. The rate of artemisinin metab. in recombinant **CYP2A6** was 15% of that for recombinant **CYP2B6**. The inhibition of artemisinin metab. in human liver microsomes by 8-methoxypsoralen (a **CYP2A6 inhibitor**) was 82% but **CYP2A6** activity was not included in the regression tree. Conclusions: Artemisinin metab. in human liver microsomes is mediated primarily by **CYP2B6** with probable secondary contribution of CYP3A4 in individuals with low **CYP2B6** expression. The contribution of **CYP2A6** to artemisinin metab. is likely of minor importance.

L15 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB ABT-378 is a potent in vitro **inhibitor** of the HIV protease and is currently being developed for coadministration with another HIV protease **inhibitor**, ritonavir, as an oral therapeutic treatment for HIV infection. In the present study, the effect of ritonavir, a potent **inhibitor** of cytochrome P 450 (CYP) 3A, on the in vitro metab. of ABT-378 was examd. Furthermore, the effect of ABT-378-ritonavir combinations on several CYP-dependent monooxygenase activities in human liver microsomes was also examd. ABT-378 was found to undergo NADPH- and CYP3A4/5-dependent metab. to three major metabolites, M-1 (4-oxo) and M-3/M-4 (4-hydroxy epimers), as well as several minor oxidative metabolites in human liver microsomes. The mean apparent Km and Vmax values for the metab. of ABT-378 by human liver microsomes were 6.8 .+-. 3.6 .mu.M and 9.4 .+-. 5.5 nmol of ABT-378 metabolized/mg protein/min, resp. Ritonavir inhibited human liver microsomal metab. of ABT-378 potently (K1 = 0.013 .mu.M). The combination of ABT-378 and ritonavir was much weaker in inhibiting CYP-mediated biotransformations than ritonavir alone, and the inhibitory effect appears to be primarily due to the ritonavir component of the combination. The ABT-378-ritonavir combinations (at 3:1 and 29:1 ratios) inhibited CYP3A (IC50 = 1.1 and 4.6 .mu.M), albeit less potently than ritonavir (IC50 = 0.14 .mu.M). Metabolic reactions mediated by CYP1A2, **CYP2A6**, and CYP2E1 were not affected by the ABT-378-ritonavir combinations. The inhibitory effects of ABT-378-ritonavir combinations on **CYP2B6** (IC50 = >30 .mu.M), CYP2C9 (IC50 = 13.7 and 23.0 .mu.M), CYP2C19 (IC50 = 28.7 and 38.0 .mu.M), and CYP2D6 (IC50 = 13.5 and 29.0 .mu.M) were marginal and are not likely to produce clin. significant drug-drug interactions.

ACCESSION NUMBER: 1999:494357 CAPLUS
DOCUMENT NUMBER: 131:266510
TITLE: Potent inhibition of the cytochrome P-450 3A-mediated human liver microsomal metabolism of a novel HIV protease inhibitor by ritonavir: a positive drug-drug interaction
AUTHOR(S): Kumar, Gondi N.; Dykstra, Jennifer; Roberts, Ellen M.; Jayanti, Venkata K.; Hickman, Dean; Uchic, John; Yao, Ye; Surber, Bruce; Thomas, Samuel; Granneman, G. Richard

CORPORATE SOURCE: Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL, 60064, USA
SOURCE: Drug Metab. Dispos. (1999), 27(8), 902-908
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Drug Metab. Dispos. (1999), 27(8), 902-908
CODEN: DMDSAI; ISSN: 0090-9556

AB ABT-378 is a potent in vitro **inhibitor** of the HIV protease and is currently being developed for coadministration with another HIV protease **inhibitor**, ritonavir, as an oral therapeutic treatment for HIV infection. In the present study, the effect of ritonavir, a potent **inhibitor** of cytochrome P 450 (CYP) 3A, on the in vitro metab. of ABT-378 was examd. Furthermore, the effect of ABT-378-ritonavir combinations on several CYP-dependent monooxygenase activities in human liver microsomes was also examd. ABT-378 was found to undergo NADPH- and CYP3A4/5-dependent metab. to three major metabolites, M-1 (4-oxo) and M-3/M-4 (4-hydroxy epimers), as well as several minor oxidative metabolites in human liver microsomes. The mean apparent Km and Vmax values for the metab. of ABT-378 by human liver microsomes were 6.8 .+-. 3.6 .mu.M and 9.4 .+-. 5.5 nmol of ABT-378 metabolized/mg protein/min, resp. Ritonavir inhibited human liver microsomal metab. of ABT-378 potently (K1 = 0.013 .mu.M). The combination of ABT-378 and ritonavir was much weaker in inhibiting CYP-mediated biotransformations than ritonavir alone, and the inhibitory effect appears to be primarily due to the ritonavir component of the combination. The ABT-378-ritonavir combinations (at 3:1 and 29:1 ratios) inhibited CYP3A (IC50 = 1.1 and 4.6 .mu.M), albeit less potently than ritonavir (IC50 = 0.14 .mu.M). Metabolic reactions mediated by CYP1A2, **CYP2A6**, and CYP2E1 were not affected by the ABT-378-ritonavir combinations. The inhibitory effects of ABT-378-ritonavir combinations on **CYP2B6** (IC50 = >30 .mu.M), CYP2C9 (IC50 = 13.7 and 23.0 .mu.M), CYP2C19 (IC50 = 28.7 and 38.0 .mu.M), and CYP2D6 (IC50 = 13.5 and 29.0 .mu.M) were marginal and are not likely to produce clin. significant drug-drug interactions.

L15 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB Fluvastatin, a 3-hydroxy-3-methylglutaryl CoA reductase **inhibitor**, was metabolized by human liver microsomes to 5-hydroxy-, 6-hydroxy-, and N-deisopropyl-fluvastatin. Total metabolite formation was biphasic with apparent Km values of 0.2 to 0.7 and 7.9 to 50 .mu.M and intrinsic metabolic clearance rates of 1.4 to 4 and 0.3 to 1.5 mL/h/mg microsomal protein for the high and low Km components, resp. Several enzymes, but mainly CYP2C9, catalyzed fluvastatin metab. Only CYP2C9 inhibitors such as sulfaphenazole inhibited the formation of both 6-hydroxy- and N-deisopropyl-fluvastatin. 5-Hydroxy-fluvastatin formation was reduced by compds. that are inhibitors of CYP2C9, CYP3A, or CYP2C8. Fluvastatin in turn inhibited CYP2C9-catalyzed tolbutamide and diclofenac hydroxylation with Ki values of 0.3 and 0.5 .mu.M, resp. For CYP2C8-catalyzed 6.alpha.-hydroxy-paclitaxel formation the IC50 was 20 .mu.M and for CYP1A2, CYP2C19, and CYP3A catalyzed reactions, no IC50 could be detd. up to 100 .mu.M fluvastatin. All three fluvastatin metabolites were also formed by recombinant CYP2C9, whereas CYP1A1, CYP2C8, CYP2D6, and CYP3A4 produced only 5-hydroxy-fluvastatin. Km values were .apprx.1, 2.8, and 7.1 .mu.M for CYP2C9, CYP2C8, and CYP3A, resp. No difference in

fluvastatin metab. was found between the CYP2C9R144 and CYP2C9C144 alleles, suggesting the absence of polymorphic fluvastatin metab. by these alleles. CYP1A2, **CYP2A6**, **CYP2B6**, CYP2C19, CYP2E1, and CYP3A5 did not produce detectable amts. of any metabolite. This data indicates that several human cytochrome P 450 enzymes metabolize fluvastatin with CYP2C9 contributing 50-80%. Any coadministered drug would therefore only partially reduce the metabolic clearance of fluvastatin; therefore, the likelihood for serious metabolic drug interactions is expected to be minimal.

ACCESSION NUMBER: 1999:169745 CAPLUS
DOCUMENT NUMBER: 130:346833
TITLE: The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor fluvastatin: effect on human cytochrome P-450 and implications for metabolic drug interactions
AUTHOR(S): Fischer, Volker; Johanson, Laurie; Heitz, Francis; Tullman, Robert; Graham, Elizabeth; Baldeck, Jean-Pierre; Robinson, William T.
CORPORATE SOURCE: Drug Metabolism and Pharmacokinetics, Novartis Institute for Biomedical Research, East Hanover, NJ, 07936, USA
SOURCE: Drug Metab. Dispos. (**1999**), 27(3), 410-416
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Drug Metab. Dispos. (**1999**), 27(3), 410-416
CODEN: DMDSAI; ISSN: 0090-9556

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L15 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB The metab. of Zaleplon (CL-284,846; ZAL) has been studied in human liver microsomal prepn. and in cDNA-expressed human cytochrome P 450 (CYP) isoforms. Human liver microsomes catalyzed the NADPH-dependent N-deethylation of ZAL to DZAL (Cl-284,859), but not to two other known in vivo metabolites, namely M1 (Cl-345,644) and M2 (CL-345,905). Sigmoidal kinetic plots were obsd. for ZAL deethylation indicating pos. cooperativity. The metab. of ZAL to DZAL was detd. in a characterized bank of 24 human liver microsomal prepns. Good correlations (r2 = 0.734-0.937) were obsd. with caffeine 8-hydroxylase, diazepam 3-hydroxylase, dextromethorphan N-demethylase and testosterone 2.beta.-, 6.beta.- and 15.beta.-hydroxylase activities, which are all catalyzed by CYP3A isoforms. In contrast, poor correlations (r2 = 0.152-0.428) were obsd. for enzymic markers for CYP1A2, **CYP2A6**, CYP2C9/10, CYP2D6, CYP2E1 and CYP4A9/11. The metab. of ZAL to DZAL in human liver microsomes was inhibited to 6-15% of control by 5-50 .mu.M of the mechanism-based CYP3A **inhibitor** troleandomycin. Whereas some inhibition of DZAL formation was obsd. in the presence of 200 .mu.M diethyldithiocarbamate, 5-50 .mu.M sulphaphenazole, 50-500 .mu.M S-mephenytoin and 1-10 .mu.M quinidine had little effect. Using human B-lymphoblastoid cell microsomes contg. cDNA-expressed CYP isoforms, ZAL was metabolized to DZAL by CYP3A4, but not to any great extent by CYP1A2, **CYP2A6**, **CYP2B6**, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1. In contrast with ZAL, the NADPH-dependent N- deethylation of M2 to M1 proceeded at only a very low rate with both human liver microsomes and cDNA-expressed CYP3A4. In summary, by correlation anal. chem. inhibition studies and the use of cDNA-expressed CYPs, ZAL N-deethylation to DZAL in human liver appears to be catalyzed by CYP3A isoforms.

ACCESSION NUMBER: 1998:301756 CAPLUS
DOCUMENT NUMBER: 129:49165
TITLE: Metabolism of zaleplon by human hepatic microsomal cytochrome P450 isoforms
AUTHOR(S): Renwick, a. B.; Mistry, H.; Ball, S. E.; Walters, D. G.; Kao, J.; Lake, B. G.
CORPORATE SOURCE: BIBRA International, Carshalton, SM5 4DS, UK
SOURCE: Xenobiotica (**1998**), 28(4), 337-348
CODEN: XENOBH; ISSN: 0049-8254
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Xenobiotica (**1998**), 28(4), 337-348
CODEN: XENOBH; ISSN: 0049-8254

AB The metab. of Zaleplon (CL-284,846; ZAL) has been studied in human liver microsomal prepn. and in cDNA-expressed human cytochrome P 450 (CYP) isoforms. Human liver microsomes catalyzed the NADPH-dependent N-deethylation of ZAL to DZAL (Cl-284,859), but not to two other known in vivo metabolites, namely M1 (Cl-345,644) and M2 (CL-345,905). Sigmoidal kinetic plots were obsd. for ZAL deethylation indicating pos. cooperativity. The metab. of ZAL to DZAL was detd. in a characterized bank of 24 human liver microsomal prepns. Good correlations (r2 = 0.734-0.937) were obsd. with caffeine 8-hydroxylase, diazepam 3-hydroxylase, dextromethorphan N-demethylase and testosterone 2.beta.-, 6.beta.- and 15.beta.-hydroxylase activities, which are all catalyzed by CYP3A isoforms. In contrast, poor correlations (r2 = 0.152-0.428) were obsd. for enzymic markers for CYP1A2, **CYP2A6**, CYP2C9/10, CYP2D6, CYP2E1 and CYP4A9/11. The metab. of ZAL to DZAL in human liver microsomes was inhibited to 6-15% of control by 5-50 .mu.M of the mechanism-based CYP3A **inhibitor** troleandomycin. Whereas some inhibition of DZAL

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L15 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB RP 73401 is a potent **inhibitor** of cyclic nucleotide phosphodiesterase type IV. RP 73401 is metabolized by human liver microsomes almost exclusively by trans-hydroxylation of the cyclopentyl group to RPR 113406. Liq. chromatog./mass spectrometry/mass spectrometry anal. of plasma from patients given RP 73401 also revealed a mol. ion and fragmentation consistent with RPR 113406. Thus, the objective was to det. the oxidative enzyme(s) responsible for RP 73401 hydroxylation. Kinetic consts. of RP 113406 formation ranged from 8 to 26 .mu.M and 0.83 to 5.99 nmol/min/mg protein for Km and Vmax, resp. Enzyme activity varied 23-fold among 15 human liver microsome samples and correlated with **CYP2A6** -catalyzed coumarin hydroxylase (r2 = 0.85) and **CYP2B6**-catalyzed 7-ethoxytrifluoromethylcoumarin O-deethylase (r2 = 0.82) activities. Chem. inhibition studies showed a 63% decrease in RP 73401 hydroxylation by 500 .mu.M orphenadrine. Coumarin (10 .mu.M), however, did not inhibit RP 73401 hydroxylation. Also, anti-CYP2B1 IgG produced 85% inhibition of RP 73401 hydroxylation, but only a negligible decline in coumarin hydroxylase activity. Of the 10 expressed P 450 forms studied, only **CYP2B6** catalyzed RP 73401 hydroxylation. Finally, expressed **CYP2B6** showed a high affinity (Km = 22.5 .mu.M) for RP 73401 hydroxylation, similar to the human liver microsome studies.

ACCESSION NUMBER: 1997:645668 CAPLUS
DOCUMENT NUMBER: 127:325908
TITLE: Human liver CYP2B6-catalyzed hydroxylation of RP 73401
AUTHOR(S): Stevens, Jeffrey C.; White, Rebecca B.; Hsu, Shih Hsein; Martinet, Michel
CORPORATE SOURCE: Department of Drug Metabolism and Pharmacokinetics, Rhone-Poulenc Rorer, Collegeville, PA, USA
SOURCE: J. Pharmacol. Exp. Ther. (**1997**), 282(3), 1389-1395
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

SO J. Pharmacol. Exp. Ther. (**1997**), 282(3), 1389-1395
CODEN: JPETAB; ISSN: 0022-3565

AB RP 73401 is a potent **inhibitor** of cyclic nucleotide phosphodiesterase type IV. RP 73401 is metabolized by human liver microsomes almost exclusively by trans-hydroxylation of the cyclopentyl group to RPR 113406. Liq. chromatog./mass spectrometry/mass spectrometry anal. of plasma from patients given RP 73401 also revealed a mol. ion and fragmentation consistent with RPR 113406. Thus, the objective was to det. the oxidative enzyme(s) responsible for RP 73401 hydroxylation. Kinetic consts. of RP 113406 formation ranged from 8 to 26 .mu.M and 0.83 to 5.99 nmol/min/mg protein for Km and Vmax, resp. Enzyme activity varied 23-fold among 15 human liver microsome samples and correlated with **CYP2A6**

-catalyzed coumarin hydroxylase (r2 = 0.85) and **CYP2B6**-catalyzed 7-ethoxytrifluoromethylcoumarin O-deethylase (r2 = 0.82) activities. Chem. inhibition studies showed a 63% decrease in RP 73401 hydroxylation by 500 .mu.M orphenadrine. Coumarin (10 .mu.M), however, did not inhibit RP 73401 hydroxylation. Also, anti-CYP2B1 IgG produced 85% inhibition of RP 73401 hydroxylation, but only a negligible decline in coumarin hydroxylase activity. Of the 10 expressed P 450 forms studied, only **CYP2B6** catalyzed RP 73401 hydroxylation. Finally, expressed **CYP2B6** showed a high affinity (Km = 22.5 .mu.M) for RP 73401 hydroxylation, similar to the human liver microsome studies.

L15 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB Studies to assess the enzyme kinetic behavior and to identify the cytochrome P 450 (CYP) isoform(s) involved in the major metabolic pathway (N-demethylation) for citalopram (CIT), a selective serotonin reuptake **inhibitor**, were performed using human liver microsomes and cDNA-expressed human cytochrome P 450 isoforms. The N-demethylation activities showed significant correlations with the .alpha.- and 4-hydroxylation activities of triazolam (rs = 0.818 and 0.851, resp.) in 10 different human liver microsomes. Anti-CYP3A antibodies and ketoconazole strongly inhibited CIT N-demethylation. In addn., there was a significant correlation between CIT N-demethylation and (S)-mephenytoin 4'-hydroxylation (rs = 0.773), although little inhibition was obsd. in the presence of anti-CYP2C antibodies or (S)-mephenytoin. CDNA-expressed CYP3A4 and CYP2C19 catalyzed CIT N-demethylation, whereas no appreciable activities were obsd. for CYP1A2, **CYP2A6**, **CYP2B6**, CYP2C9, CYP2D6 and CYP2E1. The percentage contributions of CYP3A4 and CYP2C19 to the overall N-demethylation of CIT in human liver microsomes were estd. using a relative activity factor; resp. values of 70% and 7% were calcd. for microsomes obtained from livers from putative extensive metabolizers for (S)-mephenytoin 4'-hydroxylation. These results suggest that CYP3A4 is the major isoenzyme and CYP2C19 is the minor form involved in the major metabolic pathway for CIT in human liver microsomes.

ACCESSION NUMBER:	1997:281914 CAPLUS
DOCUMENT NUMBER:	126:338339
TITLE:	Identification of cytochrome P450 isoforms involved in citalopram N-demethylation by human liver microsomes
AUTHOR(S):	Kobayashi, Kaoru; Chiba, Kan; Yagi, Tomomi; Shimada, Noriaki; Taniguchi, Tomoyoshi; Horie, Toru; Tani, Masayoshi; Yamamoto, Toshinori; Ishizaki, Takashi; Kuroiwa, Yukio
CORPORATE SOURCE:	Dep. of Clinical Pharmacy, School of Pharmaceutical Sciences, Showa University, Tokyo, Japan
SOURCE:	J. Pharmacol. Exp. Ther. (1997), 280(2), 927-933 CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER:	Williams & Wilkins
DOCUMENT TYPE:	Journal
LANGUAGE:	English

SO J. Pharmacol. Exp. Ther. (**1997**), 280(2), 927-933
CODEN: JPETAB; ISSN: 0022-3565

AB Studies to assess the enzyme kinetic behavior and to identify the cytochrome P 450 (CYP) isoform(s) involved in the major metabolic pathway (N-demethylation) for citalopram (CIT), a selective serotonin reuptake **inhibitor**, were performed using human liver microsomes and cDNA-expressed human cytochrome P 450 isoforms. The N-demethylation activities showed significant correlations with the .alpha.- and 4-hydroxylation activities of triazolam (rs = 0.818 and 0.851, resp.) in

10 different human liver microsomes. Anti-CYP3A antibodies and ketoconazole strongly inhibited CIT N-demethylation. In addn., there was a significant correlation between CIT N-demethylation and (S)-mephenytoin 4'-hydroxylation (rs = 0.773), although little inhibition was obsd. in the presence of anti-CYP2C antibodies or (S)-mephenytoin. CDNA-expressed CYP3A4 and CYP2C19 catalyzed CIT N-demethylation, whereas no appreciable activities were obsd. for CYP1A2, **CYP2A6**, **CYP2B6**, CYP2C9, CYP2D6 and CYP2E1. The percentage contributions of CYP3A4 and CYP2C19 to the overall N-demethylation of CIT in human liver microsomes were estd. using a relative activity factor; resp. values of 70% and 7% were calcd. for microsomes obtained from livers from putative extensive metabolizers for (S)-mephenytoin 4'-hydroxylation. These results suggest that CYP3A4 is the major isoenzyme and CYP2C19 is the minor form involved in the major metabolic pathway for CIT in human liver microsomes.

L15 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB The specificities of orphenadrine and methimazole on eight human liver P 450 enzyme activities were evaluated by studying the extent of inhibition at different concns. in two protocols: competitive inhibition and preincubation. In the competitive inhibition protocol, orphenadrine decreased **CYP2B6** marker activity up to 45-57% in human liver microsomes and up to 80-97% in cell microsomes contg. cDNA-expressed **CYP2B6**. Orphenadrine strongly decreased CYP2D6 marker activity by 80-90%. Orphenadrine also partially decreased the CYP1A2, **CYP2A6**, CYP3A4, and CYP2C19 marker activities. In the preincubation protocol, orphenadrine decreased the **CYP2B6** activity in cDNA-expressed cell microsomes to completion. In human liver microsomes, orphenadrine strongly decreased the marker activities of **CYP2B6**, CYP2D6, as well as CYP2C9; and partially decreased the marker activities of CYP1A2, **CYP2A6**, CYP3A4, and CYP2C19. In the competitive inhibition protocol, methimazole had no effect on the marker activities of CYP2E1 and **CYP2A6**; slightly decreased CYP2D6 marker activity; partially decreased the marker activities of CYP2C19, CYP2C9, and **CYP2B6**; and dramatically decreased CYP3A4 marker activity. Methimazole decreased CYP1A2 marker activity at lower concns., but not at the highest concn. studied (1 mM). In the preincubation protocol, methimazole was shown to be a potent and nonspecific **inhibitor** of all the enzyme activities. Marker activities of CYP2C9, CYP2C19, and CYP3A4 were completely inhibited at relatively low concns. This study indicates orphenadrine cannot be used as a selective **inhibitor** of **CYP2B6** in human liver microsomes and that methimazole is not a selective **inhibitor** of the flavin-contg. monooxygenase in human liver microsomes.

ACCESSION NUMBER: 1997:193442 CAPLUS
DOCUMENT NUMBER: 126:272187
TITLE: Orphenadrine and methimazole inhibit multiple cytochrome P450 enzymes in human liver microsomes
AUTHOR(S): Guo, Zuyu; Raeissi, Shamsi; White, Rebecca B.; Stevens, Jeffrey C.
CORPORATE SOURCE: Dep. Drug Metab. Pharmacokinetics, Rhone-Poulenc Rorer, Collegeville, PA, 19426, USA
SOURCE: Drug Metab. Dispos. (**1997**), 25(3), 390-393
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Drug Metab. Dispos. (**1997**), 25(3), 390-393
CODEN: DMDSAI; ISSN: 0090-9556

AB The specificities of orphenadrine and methimazole on eight human liver P 450 enzyme activities were evaluated by studying the extent of inhibition at different concns. in two protocols: competitive inhibition and preincubation. In the competitive inhibition protocol, orphenadrine decreased **CYP2B6** marker activity up to 45-57% in human liver microsomes and up to 80-97% in cell microsomes contg. cDNA-expressed **CYP2B6**. Orphenadrine strongly decreased CYP2D6 marker activity by 80-90%. Orphenadrine also partially decreased the CYP1A2, **CYP2A6** , CYP3A4, and CYP2C19 marker activities. In the preincubation protocol, orphenadrine decreased the **CYP2B6** activity in cDNA-expressed cell microsomes to completion. In human liver microsomes, orphenadrine strongly decreased the marker activities of **CYP2B6**, CYP2D6, as well as CYP2C9; and partially decreased the marker activities of CYP1A2, **CYP2A6**, CYP3A4, and CYP2C19. In the competitive inhibition protocol, methimazole had no effect on the marker activities of CYP2E1 and **CYP2A6**; slightly decreased CYP2D6 marker activity; partially decreased the marker activities of CYP2C19, CYP2C9, and **CYP2B6**; and dramatically decreased CYP3A4 marker activity. Methimazole decreased CYP1A2 marker activity at lower concns., but not at the highest concn. studied (1 mM). In the preincubation protocol, methimazole was shown to be a potent and nonspecific **inhibitor** of all the enzyme activities. Marker activities of CYP2C9, CYP2C19, and CYP3A4 were completely inhibited at relatively low concns. This study indicates orphenadrine cannot be used as a selective **inhibitor** of **CYP2B6** in human liver microsomes and that methimazole is not a selective **inhibitor** of the flavin-contg. monooxygenase in human liver microsomes.

L15 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB Because YM17E (1,3-bis[[1-cycloheptyl-3-(p-dimethylaminophenyl)ureido]methyl]benzene dihydrochloride) inhibits acyl CoA: cholesterol acyltransferase (ACAT) it has potential application in the treatment of hypercholesterolemia. In man and animals YM17E is extensively metabolized, via N-demethylation, to five active metabolites (M1, M2-a, M2-b, M3 and M4). The main objectives of this study were to examine inhibition of YM17E metab. by the products and identify the cytochrome P 450 isoforms in liver microsomes which catalyze in-vitro YM17E metab. in man. In microsomes in man, N-demethylation of YM17E to M1 occurred enzymically; for up to 45 s the rate was linearly proportional to the microsomal protein concn. This reaction was inhibited by metabolites M2-a, M2-b, M3 and M4. Further, N-demethylation of [14C]-YM17E was also inhibited by its product, M1. These results showed that primary metab. of YM17E was inhibited by its products, and supported the finding that the non-linear increase in plasma concn. of the parent drug and metabolites obsd. in an in-vivo study was due to inhibition by these products. Metabolic activity in microsomes from ten individual human livers demonstrated that YM17E N-demethylase activity correlated closely with testosterone 6.beta.-hydroxylase activity. When cytochrome P 450 isoenzyme-specific substrates and chem. inhibitors were used to inhibit YM17E N-demethylase activity, CYP3A-specific substrate and inhibitors such as nifedipine, ketoconazole and triacetyloleandomycin strongly inhibited this activity, whereas CYP1A-specific substrate or **inhibitor**, ethoxyresorufin and .alpha.-naphthoflavone, inhibited weakly. Other CYP inhibitors, in contrast, had few or no effects. An inhibition study using anti-rat CYP1A1, CYP2B1, CYP2C11, CYP2E1 and CYP3A2 antibodies demonstrated that only anti-rat CYP3A2 antibody inhibited YM17E metab., to 40% of control level, with no other antibodies showing an inhibitory effect. Of seven cDNA-expressed P 450 isoforms in man (CYP1A1, CYP1A2,

CYP2A6, **CYP2B6**, CYP2D6, CYP2E1 and CYP3A4), CYP3A4, CYP2D6 and CYP1A2 isoenzyme exhibited substantial catalytic activity of N-demethylation of YM17E. These results indicate the predominant role of CYP3A4 in liver metab. of YM17E in man.

ACCESSION NUMBER: 1997:16561 CAPLUS
DOCUMENT NUMBER: 126:84038
TITLE: In-vitro metabolism of YM17E, an inhibitor of Acyl coenzyme A:cholesterol acyltransferase, by liver microsomes in man
AUTHOR(S): Uchida, Taisuke; Watanabe, Takashi; Van Hoogdalem, Ewoud J.; Higuchi, Saburo
CORPORATE SOURCE: Drug Metabolism Department, Clinical Pharmacology Research Laboratories, Yamanouchi Pharmaceutical Co. Ltd, Tokyo, 174, Japan
SOURCE: J. Pharm. Pharmacol. (**1996**), 48(10), 1049-1056
CODEN: JPPMAB; ISSN: 0022-3573
PUBLISHER: Royal Pharmaceutical Society of Great Britain
DOCUMENT TYPE: Journal
LANGUAGE: English

SO J. Pharm. Pharmacol. (**1996**), 48(10), 1049-1056
CODEN: JPPMAB; ISSN: 0022-3573

AB Because YM17E (1,3-bis[[1-cycloheptyl-3-(p-dimethylaminophenyl)ureido]methyl]benzene dihydrochloride) inhibits acyl CoA: cholesterol acyltransferase (ACAT) it has potential application in the treatment of hypercholesterolemia. In man and animals YM17E is extensively metabolized, via N-demethylation, to five active metabolites (M1, M2-a, M2-b, M3 and M4). The main objectives of this study were to examine inhibition of YM17E metab. by the products and identify the cytochrome P 450 isoforms in liver microsomes which catalyze in-vitro YM17E metab. in man. In microsomes in man, N-demethylation of YM17E to M1 occurred enzymically; for up to 45 s the rate was linearly proportional to the microsomal protein concn. This reaction was inhibited by metabolites M2-a, M2-b, M3 and M4. Further, N-demethylation of [14C]-YM17E was also inhibited by its product, M1. These results showed that primary metab. of YM17E was inhibited by its products, and supported the finding that the non-linear increase in plasma concn. of the parent drug and metabolites obsd. in an in-vivo study was due to inhibition by these products. Metabolic activity in microsomes from ten individual human livers demonstrated that YM17E N-demethylase activity correlated closely with testosterone 6.beta.-hydroxylase activity. When cytochrome P 450 isoenzyme-specific substrates and chem. inhibitors were used to inhibit YM17E N-demethylase activity, CYP3A-specific substrate and inhibitors such as nifedipine, ketoconazole and triacetyloleandomycin strongly inhibited this activity, whereas CYP1A-specific substrate or **inhibitor**, ethoxyresorufin and .alpha.-naphthoflavone, inhibited weakly. Other CYP inhibitors, in contrast, had few or no effects. An inhibition study using anti-rat CYP1A1, CYP2B1, CYP2C11, CYP2E1 and CYP3A2 antibodies demonstrated that only anti-rat CYP3A2 antibody inhibited YM17E metab., to 40% of control level, with no other antibodies showing an inhibitory effect. Of seven cDNA-expressed P 450 isoforms in man (CYP1A1, CYP1A2, **CYP2A6**, **CYP2B6**, CYP2D6, CYP2E1 and CYP3A4), CYP3A4, CYP2D6 and CYP1A2 isoenzyme exhibited substantial catalytic activity of N-demethylation of YM17E. These results indicate the predominant role of CYP3A4 in liver metab. of YM17E in man.

L15 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB The metab. of isoprene was investigated with microsomes derived from cell

lines expressing human CYP1A1, CYP1A2, **CYP2A6**, **CYP2B6**, CYP2C9, CYP2D6, CYP2E1, or CYP3A4. The formation of epoxide metabolites was detd. by gas chromatog. anal. CYP2E1 showed the highest rates of formation of the isoprene monoepoxides 3,4-epoxy-3-methyl-1-butene (EPOX-I) and 3,4-epoxy-2-methyl-1-butene (EPOX-II), followed by **CYP2B6**. CYP2E1 was the only enzyme showing detectable formation of the diepoxide of isoprene, 2-methyl-1,2:3,4-diepoxybutane. Both isoprene monoepoxides were oxidized by CYP2E1 to the diepoxide at similar enzymic rates. To det. the relative role of CYP2E1 in hepatic metab., isoprene as well as the two monoepoxides were also incubated with a series of ten human liver microsomal prepns. in the presence of the epoxide hydrolase **inhibitor** cyclohexene oxide. The obtained activities were correlated with activities towards specific substrates for CYP1A2, **CYP2A6**, CYP2C9, CYP2D6, CYP2E1 and CYP3A. The results were supportive for those obtained with single human P 450 enzymes. Isoprene (monoepoxide) metab. showed a significant correlation with CYP2E1 activity, detd. as chlorzoxazone 6-hydroxylation. CYP2E1 is therefore the major enzyme involved in hepatic metab. of isoprene and the isoprene monoepoxides in vitro. To investigate species differences with regard to the role of epoxide hydrolase in the metab. of isoprene monoepoxides, the epoxidn. of isoprene by human liver microsomes was compared to that of mouse and rat liver microsomes. The amts. of monoepoxides formed as a balance between epoxidn. and hydrolysis, was measured in incubations with and without the epoxide hydrolase **inhibitor** cyclohexene oxide. Inhibition of epoxide hydrolase resulted in similar rates of monoepoxide formation in mouse, rat and man. Without **inhibitor**, however, the total amt. of monoepoxides present at the end of the incubation period was twice as high for mouse liver microsomes than for rat and even 15 times as high as for human liver microsomes. Thus, differences in epoxide hydrolase activity between species may be of crucial importance for the toxicity of isoprene in the various species.

ACCESSION NUMBER: 1996:750441 CAPLUS
DOCUMENT NUMBER: 126:85785
TITLE: The biotransformation of isoprene and the two isoprene monoepoxides by human cytochrome P450 enzymes, compared to mouse and rat liver microsomes
AUTHOR(S): Bogaards, Jan J. P.; Venekamp, Joke C.; van Bladeren, Peter J.
CORPORATE SOURCE: Toxicology Division, TNO Nutrition and Food Research Institute, P.O. Box 360, AJ Zeist, 3700, Neth.
SOURCE: Chem.-Biol. Interact. (**1996**), 102(3), 169-182
CODEN: CBINA8; ISSN: 0009-2797
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Chem.-Biol. Interact. (**1996**), 102(3), 169-182
CODEN: CBINA8; ISSN: 0009-2797

AB The metab. of isoprene was investigated with microsomes derived from cell lines expressing human CYP1A1, CYP1A2, **CYP2A6**, **CYP2B6**, CYP2C9, CYP2D6, CYP2E1, or CYP3A4. The formation of epoxide metabolites was detd. by gas chromatog. anal. CYP2E1 showed the highest rates of formation of the isoprene monoepoxides 3,4-epoxy-3-methyl-1-butene (EPOX-I) and 3,4-epoxy-2-methyl-1-butene (EPOX-II), followed by **CYP2B6**. CYP2E1 was the only enzyme showing detectable formation of the diepoxide of isoprene, 2-methyl-1,2:3,4-diepoxybutane. Both isoprene monoepoxides were oxidized by CYP2E1 to the diepoxide at similar enzymic rates. To det. the relative role of CYP2E1 in hepatic metab.,

isoprene as well as the two monoepoxides were also incubated with a series of ten human liver microsomal prepns. in the presence of the epoxide hydrolase **inhibitor** cyclohexene oxide. The obtained activities were correlated with activities towards specific substrates for CYP1A2, **CYP2A6**, CYP2C9, CYP2D6, CYP2E1 and CYP3A. The results were supportive for those obtained with single human P 450 enzymes. Isoprene (monoepoxide) metab. showed a significant correlation with CYP2E1 activity, detd. as chlorzoxazone 6-hydroxylation. CYP2E1 is therefore the major enzyme involved in hepatic metab. of isoprene and the isoprene monoepoxides in vitro. To investigate species differences with regard to the role of epoxide hydrolase in the metab. of isoprene monoepoxides, the epoxidn. of isoprene by human liver microsomes was compared to that of mouse and rat liver microsomes. The amts. of monoepoxides formed as a balance between epoxidn. and hydrolysis, was measured in incubations with and without the epoxide hydrolase **inhibitor** cyclohexene oxide. Inhibition of epoxide hydrolase resulted in similar rates of monoepoxide formation in mouse, rat and man. Without **inhibitor**, however, the total amt. of monoepoxides present at the end of the incubation period was twice as high for mouse liver microsomes than for rat and even 15 times as high as for human liver microsomes. Thus, differences in epoxide hydrolase activity between species may be of crucial importance for the toxicity of isoprene in the various species.

L15 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB In vitro methods were used to identify the cytochrome P 450 (CYP) enzyme(s) involved in S-mephenytoin N-demethylation. S-mephenytoin (200 .mu.M) was incubated with human liver microsomes, and nirvanol formation was quantitated by reversed-phase HPLC. Mephenytoin N-demethylase activity in a panel of human liver microsomes ranged 35-fold from 9 to 319 pmol/min protein and correlated strongly with microsomal **CYP2B6** activity (r = 0.91). Addnl. correlation were found with microsomal **CYP2A6** and CYP3A4 activity (r = 0.88 and 0.74, resp.). Microsomes prepd. from human .beta.-lymphoblastoid cells transformed with individual P 450 cDNAs were assayed for S-mephenytoin N-demethylase activity. Of 11 P 450 isoforms (P450s 1A1, 1A2, 2A6, 2B6, 2E1, 2D6, 2C8, 2C9, 3A4, and 3A5) tested, only **CYP2B6** catalyzed the N-demethylation of S-mephenytoin with an apparent Km of 564 .mu.M. Expts. with P 450 form-selective chem. inhibitors, competitive substrates, and anti-P 450 antibodies were also performed. Troleandomycin, a mechanism-based CYP3A selective **inhibitor**, and coumarin, a substrate for **CYP2A6** and therefore a potential competitive **inhibitor**, failed to inhibit human liver microsomal S-mephenytoin N-demethylation. In contrast, orphenadrine, an **inhibitor** of CYP2B forms, produced at 51.OMEGA.4% decrease in S-mephenytoin N-demethylase activity in human liver microsomes and a 45% decrease in recombinant microsomes expressing **CYP2B6**. Also, both **CYP2B6**-marker 7-ethoxytrifluoromethylcoumarin O-deethylase and S-mephenytoin N-demethylase activities were inhibited by .apprx.65% by 5 mg anti-CYP2B1 IgG/mg microsomal protein. Finally, polyclonal antibody inhibitory to CYP3A1 failed to inhibit S-mephenytoin N-demethylase activity. Taken together, these studies indicate that the N-demethylation of S-mephenytoin by human liver microsomes is catalyzed primarily by **CYP2B6**.

ACCESSION NUMBER: 1996:589147 CAPLUS
DOCUMENT NUMBER: 125:264890
TITLE: Catalytic role of cytochrome P4502B6 in the N-demethylation of S-mephenytoin
AUTHOR(S): Heyn, Heleen; White, Rebecca B.; Stevens, Jeffrey C.
CORPORATE SOURCE: Dep. Drug Metab. Pharmacokinetics, Rhone-Poulenc Rorer

Res. Development, Collegeville, PA, 19426-0107, USA
SOURCE: Drug Metab. Dispos. (1996), 24(9), 948-954
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Drug Metab. Dispos. (1996), 24(9), 948-954
CODEN: DMDSAI; ISSN: 0090-9556

AB In vitro methods were used to identify the cytochrome P 450 (CYP) enzyme(s) involved in S-mephenytoin N-demethylation. S-mephenytoin (200 .mu.M) was incubated with human liver microsomes, and nirvanol formation was quantitated by reversed-phase HPLC. Mephenytoin N-demethylase activity in a panel of human liver microsomes ranged 35-fold from 9 to 319 pmol/min protein and correlated strongly with microsomal **CYP2B6** activity (r = 0.91). Addnl. correlation were found with microsomal **CYP2A6** and CYP3A4 activity (r = 0.88 and 0.74, resp.). Microsomes prepd. from human .beta.-lymphoblastoid cells transformed with individual P 450 cDNAs were assayed for S-mephenytoin N-demethylase activity. Of 11 P 450 isoforms (P450s 1A1, 1A2, 2A6, 2B6, 2E1, 2D6, 2C8, 2C9, 3A4, and 3A5) tested, only **CYP2B6** catalyzed the N-demethylation of S-mephenytoin with an apparent Km of 564 .mu.M. Expts. with P 450 form-selective chem. inhibitors, competitive substrates, and anti-P 450 antibodies were also performed. Troleandomycin, a mechanism-based CYP3A selective **inhibitor**, and coumarin, a substrate for **CYP2A6** and therefore a potential competitive **inhibitor**, failed to inhibit human liver microsomal S-mephenytoin N-demethylation. In contrast, orphenadrine, an **inhibitor** of CYP2B forms, produced at 51.OMEGA.4% decrease in S-mephenytoin N-demethylase activity in human liver microsomes and a 45% decrease in recombinant microsomes expressing **CYP2B6**. Also, both **CYP2B6**-marker 7-ethoxytrifluoromethylcoumarin O-deethylase and S-mephenytoin N-demethylase activities were inhibited by .apprx.65% by 5 mg anti-CYP2B1 IgG/mg microsomal protein. Finally, polyclonal antibody inhibitory to CYP3A1 failed to inhibit S-mephenytoin N-demethylase activity. Taken together, these studies indicate that the N-demethylation of S-mephenytoin by human liver microsomes is catalyzed primarily by **CYP2B6**.

L15 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB We evaluated the specificity of 15 substrates and 14 inhibitors of the cytochrome P450s using nine human P 450 isoforms expressed in HepG2 cells using a recombinant vaccinia virus and also in human liver microsomes. Coumarin, 7-ethoxyresorufin, 7-benzyloxyresorufin, tolbutamide, aniline and diazepam were isoform-selective substrates towards **CYP2A6**, the CYP1A subfamily, **CYP2B6**, the CYP2C subfamily, CYP2E1 and the CYP3A subfamily, resp. However, a selective substrate for CYP2D6 was not found among the chems. tested. SKF-525A inhibited > 40% of the metabolic activity of all substrates tested, and the inhibitory effects differed among P 450 isoforms. Sulfaphenazole, 7,8-benzoflavone, quinidine and troleandomycin were selective inhibitors of the CYP2C subfamily (except CYP2C19), the CYP1A subfamily, CYP2D6 and the CYP3A subfamily, resp. Methoxsalen (**CYP2A6 inhibitor**) inhibited the metabolic activity of CYP1A2 as well as that of **CYP2A6**. Diethyldithiocarbamate (CYP2E1 **inhibitor**) inhibited the metabolic activities of **CYP2A6** and CYP2C19 in addn. to that of CYP2E1. Our results indicated that substrates and inhibitors reported as P 450 selective probes are not necessarily specific for individual human P 450 isoforms. These results may provide useful information regarding human P 450 substrates and inhibitors in vitro using human liver microsomal samples.

ACCESSION NUMBER: 1996:424712 CAPLUS
DOCUMENT NUMBER: 125:80284
TITLE: Specificity of substrate and inhibitor probes for cytochrome P450s: evaluation of in vitro metabolism using cDNA-expressed human P450s and human liver microsomes
AUTHOR(S): Ono, S.; Hatanaka, T.; Hotta, H.; Satoh, T.; Gonzalez, F. J.; Tsutsui, M.
CORPORATE SOURCE: Amersham K.K., Central Lab. for Research and Development, Chiba, 270-14, Japan
SOURCE: Xenobiotica (**1996**), 26(7), 681-693
CODEN: XENOBH; ISSN: 0049-8254
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Xenobiotica (**1996**), 26(7), 681-693
CODEN: XENOBH; ISSN: 0049-8254
AB We evaluated the specificity of 15 substrates and 14 inhibitors of the cytochrome P450s using nine human P 450 isoforms expressed in HepG2 cells using a recombinant vaccinia virus and also in human liver microsomes. Coumarin, 7-ethoxyresorufin, 7-benzyloxyresorufin, tolbutamide, aniline and diazepam were isoform-selective substrates towards **CYP2A6**, the CYP1A subfamily, **CYP2B6**, the CYP2C subfamily, CYP2E1 and the CYP3A subfamily, resp. However, a selective substrate for CYP2D6 was not found among the chems. tested. SKF-525A inhibited > 40% of the metabolic activity of all substrates tested, and the inhibitory effects differed among P 450 isoforms. Sulfaphenazole, 7,8-benzoflavone, quinidine and troleandomycin were selective inhibitors of the CYP2C subfamily (except CYP2C19), the CYP1A subfamily, CYP2D6 and the CYP3A subfamily, resp. Methoxsalen (**CYP2A6 inhibitor**) inhibited the metabolic activity of CYP1A2 as well as that of **CYP2A6**. Diethyldithiocarbamate (CYP2E1 **inhibitor**) inhibited the metabolic activities of **CYP2A6** and CYP2C19 in addn. to that of CYP2E1. Our results indicated that substrates and inhibitors reported as P 450 selective probes are not necessarily specific for individual human P 450 isoforms. These results may provide useful information regarding human P 450 substrates and inhibitors in vitro using human liver microsomal samples.

L15 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2002 ACS
AB Cytochrome P 450 (CYP) activity in human liver microsomes was measured after the O-demethylation of [O-Me 14C]naproxen (NAPase). The formation of [14C]formaldehyde in the presence of microsomes was described by an apparent KM(1) and Vmax(1) of 0.16 mM and 4.1 nmol HCHO/min/mg protein (mean; N = 5 different livers), resp., over a relatively wide naproxen concn. (5-1600 .mu.M) range. With two sets of microsomes, a high KM NAPase component was also detected (mean KM2 = 2.7 mM; mean Vmax2 = 23 nmol HCHO/min/mg). As expected, the O-demethylation of naproxen (0.4 mM) was highly correlated with tolbutamide hydroxylase (TOLase) activity in a panel of human liver microsomes (r = 0.82, N = 10) and was inhibited (32-54%) by a no. of purported CYP2C (CYP2C9/10) inhibitors/substrates (e.g. phenytoin, sulfaphenazole, tienilic acid, tolbutamide, and ibuprofen). Only marginal decreases in activity (.ltoreq.14%) were obsd. with inhibitors of other CYP proteins. However, NAPase activity was also found to correlate significantly with CYP1A2 [ethoxyresorufin O-deethylase (ERODase)] activity (r = 0.68). In addn., the reaction was inhibited (36-75%, N = 11 different livers) by furafylline (FURA), a CYP1A2-selective mechanism-based **inhibitor**. The effect of FURA and tienilic acid was additive, leading to 90% inhibition of NAPase

activity. FURA-inhibited activity also significantly correlated with ERODase activity (r = 0.78, N = 11), whereas tienilic acid-inhibited activity correlated with TOLase activity (r = 0.63, N = 10). In human B-lymphoblast microsomes, cDNA-expressed CYP1AS2 exhibited relatively high activity (KM = 0.25 mM; Vmax = 24 nmol/min/nmol CYP), when compared with **CYP2A6**, CYP2D6, CYP2E1, **CYP2B6**, and CYP3A4. The kinetic parameters for reconstituted purified human liver microsomal CYP2C9 (KM = 0.43 mM; Vmax = 11 nmol/min/nmol CYP) were comparable with those of CYP1A2. It is concluded that the O-demethylation of naproxen (.ltoreq.0.4 mM) is catalyzed by CYP2C subfamily members (CYP2C9/10) and CYP1A2 in human liver microsomes.

ACCESSION NUMBER: 1996:70852 CAPLUS
DOCUMENT NUMBER: 124:249528
TITLE: [O-Methyl-18C]naproxen O-demethylase activity in human liver microsomes. Evidence for the involvement of cytochrome P4501A2 and P4502C9/10
AUTHOR(S): Rodrigues, A. David; Kukulka, Michael J.; Roberts, Ellen M.; Ouellet, Daniele; Rodgers, Thomas R.
CORPORATE SOURCE: Drug Metabolism Dep., Abbott Laboratories, Abbott Park, IL, 60064, USA
SOURCE: Drug Metab. Dispos. (**1996**), 24(1), 126-36
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Drug Metab. Dispos. (**1996**), 24(1), 126-36
CODEN: DMDSAI; ISSN: 0090-9556
AB Cytochrome P 450 (CYP) activity in human liver microsomes was measured after the O-demethylation of [O-Me 14C]naproxen (NAPase). The formation of [14C]formaldehyde in the presence of microsomes was described by an apparent KM(1) and Vmax(1) of 0.16 mM and 4.1 nmol HCHO/min/mg protein (mean; N = 5 different livers), resp., over a relatively wide naproxen concn. (5-1600 .mu.M) range. With two sets of microsomes, a high KM NAPase component was also detected (mean KM2 = 2.7 mM; mean Vmax2 = 23 nmol HCHO/min/mg). As expected, the O-demethylation of naproxen (0.4 mM) was highly correlated with tolbutamide hydroxylase (TOLase) activity in a panel of human liver microsomes (r = 0.82, N = 10) and was inhibited (32-54%) by a no. of purported CYP2C (CYP2C9/10) inhibitors/substrates (e.g. phenytoin, sulfaphenazole, tienilic acid, tolbutamide, and ibuprofen). Only marginal decreases in activity (.ltoreq.14%) were obsd. with inhibitors of other CYP proteins. However, NAPase activity was also found to correlate significantly with CYP1A2 [ethoxyresorufin O-deethylase (ERODase)] activity (r = 0.68). In addn., the reaction was inhibited (36-75%, N = 11 different livers) by furafylline (FURA), a CYP1A2-selective mechanism-based **inhibitor**. The effect of FURA and tienilic acid was additive, leading to 90% inhibition of NAPase activity. FURA-inhibited activity also significantly correlated with ERODase activity (r = 0.78, N = 11), whereas tienilic acid-inhibited activity correlated with TOLase activity (r = 0.63, N = 10). In human B-lymphoblast microsomes, cDNA-expressed CYP1AS2 exhibited relatively high activity (KM = 0.25 mM; Vmax = 24 nmol/min/nmol CYP), when compared with **CYP2A6**, CYP2D6, CYP2E1, **CYP2B6**, and CYP3A4. The kinetic parameters for reconstituted purified human liver microsomal CYP2C9 (KM = 0.43 mM; Vmax = 11 nmol/min/nmol CYP) were comparable with those of CYP1A2. It is concluded that the O-demethylation of naproxen (.ltoreq.0.4 mM) is catalyzed by CYP2C subfamily members (CYP2C9/10) and CYP1A2 in human liver microsomes.

L15 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB The present study investigated the role of rat and human cytochrome P 450 enzymes in the sulfoxidn. of S-Me N,N-diethylthiolcarbamate (DETC-Me) to S-Me N,N-diethylthiolcarbamate sulfoxide (DETC-Me sulfoxide), the putative active metabolite of disulfiram. DETC-Me sulfoxidn. by microsomes from male and female rats treated with various cytochrome P 450-enzyme inducers suggested that multiple enzymes can catalyze this reaction, and these include, CYP1A1/2, CYP2B1/2, and CYP3A1/2. All cDNA-expressed human cytochrome P 450 enzymes examd. catalyzed the sulfoxidn. of DETC-Me. The turnover rates (min-1) of DETC-Me sulfoxidn. by the cDNA-expressed cytochrome P 450 enzymes ranked as follows: CYP3A4 > **CYP2A6** - CYP2C9 > CYP1A2 > **CYP2B6** - CYP2E1 > CYP1A1 > CYP2D6. Interestingly, CYP3A4 ranked first or last, depending on whether or not addnl. NADPH-cytochrome P 450 reductase was coexpressed in the lymphoblastoid cells. This complicated ests. of the contribution of CYP3A4 to DETC-Me sulfoxidn. by human liver microsomes. The sample-to-sample variation in DETC-Me sulfoxidn. by a bank of human liver microsomes (N = 13) correlated highly with coumarin 7-hydroxylation (r = 0.88) and testosterone 6.beta.-hydroxylation (r = 0.90), suggesting that **CYP2A6** and CYP3A4/5 contribute to the sulfoxidn. of DETC-Me by human liver microsomes. Although, chlorzoxazone 6-hydroxylation (a marker for CYP2E1) correlated poorly with DETC-Me sulfoxidn., the correlation improved from r = 0.07 to r = 0.44 when DETC-Me sulfoxidn. was studied in the presence of the **CYP2A6 inhibitor**, coumarin.

Similarly, when DETC-Me sulfoxidn. was studied in the presence of diethyldithiocarbamate (DDTC), the inhibited DETC-Me sulfoxidase activity correlated better (r = 0.50) with chlorzoxazone 6-hydroxylase, compared with DETC-Me sulfoxidase activity in the absence of DDTC (r = 0.09). Polyclonal antibodies against CYP2E1 caused a modest inhibition (30%) of DETC-Me sulfoxidn. by human liver microsomes. Anti-CYP3A1 antibodies completely inhibited DETC-Me sulfoxidn. by cDNA-expressed CYP3A4. Under similar conditions, DETC-Me sulfoxidn. by human liver microsomes was only partially inhibited by anti-CYP3A1 antibodies. Although studies with the rat and cDNA-expressed cytochrome P 450 enzymes suggested that CYP1A2 contributed to DETC-Me sulfoxidn., this reaction was not inhibited by either furafylline (a mechanism-based **inhibitor** of CYP1A2) or antibodies against CYP1A1/2. A significant role for CYP2C9 was excluded by the inability of sulfaphenazole to inhibit the sulfoxidn. of DETC-Me by human liver microsomes. Collectively, these data suggest that multiple cytochrome P 450 enzymes can catalyze the sulfoxidn. of DETC-Me. In human liver microsomes the **CYP2A6**, CYP2E1, and CYP3A4/5 all contribute significantly to the sulfoxidn. of DETC-Me. It is interesting to note that DDTC, the reduced metabolite of disulfiram, is known to inhibit these same enzymes. The ability of DDTC to block the formation of DETC-Me sulfoxide may explain why the dose of disulfiram required to produce a disulfiram-ethanol reaction in alcoholics is so variable and often inadequate.

ACCESSION NUMBER: 1995:895750 CAPLUS
DOCUMENT NUMBER: 123:333330
TITLE: Identification of the human and rat P450 enzymes responsible for the sulfoxidation of S-methyl N,N-diethylthiolcarbamate (DETC-ME): the terminal step in the bioactivation of disulfiram
AUTHOR(S): Madan, Ajay; Parkinson, Andrew; Faiman, Morris D.
CORPORATE SOURCE: Department Pharmacology, Toxicology, University Kansas, Lawrence, KS, 66045, USA
SOURCE: Drug Metab. Dispos. (**1995**), 23(10), 1153-62
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal

LANGUAGE: English
SO Drug Metab. Dispos. (1995), 23(10), 1153-62
CODEN: DMDSAI; ISSN: 0090-9556

AB The present study investigated the role of rat and human cytochrome P 450 enzymes in the sulfoxidn. of S-Me N,N-diethylthiolcarbamate (DETC-Me) to S-Me N,N-diethylthiolcarbamate sulfoxide (DETC-Me sulfoxide), the putative active metabolite of disulfiram. DETC-Me sulfoxidn. by microsomes from male and female rats treated with various cytochrome P 450-enzyme inducers suggested that multiple enzymes can catalyze this reaction, and these include, CYP1A1/2, CYP2B1/2, and CYP3A1/2. All cDNA-expressed human cytochrome P 450 enzymes examd. catalyzed the sulfoxidn. of DETC-Me. The turnover rates (min-1) of DETC-Me sulfoxidn. by the cDNA-expressed cytochrome P 450 enzymes ranked as follows: CYP3A4 > **CYP2A6** - CYP2C9 > CYP1A2 > **CYP2B6** - CYP2E1 > CYP1A1 > CYP2D6. Interestingly, CYP3A4 ranked first or last, depending on whether or not addnl. NADPH-cytochrome P 450 reductase was coexpressed in the lymphoblastoid cells. This complicated ests. of the contribution of CYP3A4 to DETC-Me sulfoxidn. by human liver microsomes. The sample-to-sample variation in DETC-Me sulfoxidn. by a bank of human liver microsomes (N = 13) correlated highly with coumarin 7-hydroxylation (r = 0.88) and testosterone 6.beta.-hydroxylation (r = 0.90), suggesting that **CYP2A6** and CYP3A4/5 contribute to the sulfoxidn. of DETC-Me by human liver microsomes. Although, chlorzoxazone 6-hydroxylation (a marker for CYP2E1) correlated poorly with DETC-Me sulfoxidn., the correlation improved from r = 0.07 to r = 0.44 when DETC-Me sulfoxidn. was studied in the presence of the **CYP2A6 inhibitor**, coumarin. Similarly, when DETC-Me sulfoxidn. was studied in the presence of diethyldithiocarbamate (DDTC), the inhibited DETC-Me sulfoxidase activity correlated better (r = 0.50) with chlorzoxazone 6-hydroxylase, compared with DETC-Me sulfoxidase activity in the absence of DDTC (r = 0.09). Polyclonal antibodies against CYP2E1 caused a modest inhibition (30%) of DETC-Me sulfoxidn. by human liver microsomes. Anti-CYP3A1 antibodies completely inhibited DETC-Me sulfoxidn. by cDNA-expressed CYP3A4. Under similar conditions, DETC-Me sulfoxidn. by human liver microsomes was only partially inhibited by anti-CYP3A1 antibodies. Although studies with the rat and cDNA-expressed cytochrome P 450 enzymes suggested that CYP1A2 contributed to DETC-Me sulfoxidn., this reaction was not inhibited by either furafylline (a mechanism-based **inhibitor** of CYP1A2) or antibodies against CYP1A1/2. A significant role for CYP2C9 was excluded by the inability of sulfaphenazole to inhibit the sulfoxidn. of DETC-Me by human liver microsomes. Collectively, these data suggest that multiple cytochrome P 450 enzymes can catalyze the sulfoxidn. of DETC-Me. In human liver microsomes the **CYP2A6**, CYP2E1, and CYP3A4/5 all contribute significantly to the sulfoxidn. of DETC-Me. It is interesting to note that DDTC, the reduced metabolite of disulfiram, is known to inhibit these same enzymes. The ability of DDTC to block the formation of DETC-Me sulfoxide may explain why the dose of disulfiram required to produce a disulfiram-ethanol reaction in alcoholics is so variable and often inadequate.

L15 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB The membrane-bound endogenous fatty acid arachidonic acid can be released from membranes by phospholipases and then metabolized to biol. active compds. by cyclooxygenases, lipoxygenases, and cytochrome P 450 (CYP) enzymes. In the liver the CYP pathway is the most significant. Liver CYP arachidonate products include epoxyeicosatrienoic acids (EETs) and monohydroxylated products (HETEs). The authors examd. metab. of [1-14C]arachidonic acid by a panel of 10 human CYP enzymes expressed in

HepG2 cells. In the absence of expressed CYP enzymes, control HepG2 cell microsomes generated only small amts. of .omega.- and .omega. - 1-OH arachidonic acid (ratio 2:1). Microsomes from HepG2 cells expressing CYP2C8, 2C9, 1A2, and 2E1 were 7-21 times more active than microsomes from the HepG2 controls. CYP2C8, 2C9, and 1A2 principally generated epoxygenase products; 36 to 48% were in the form of EET-diols, reflecting host HepG2 microsomal epoxide hydrolase activity. CYP2C8 and 2C9 formed more 14,15- and 11,12-EET than did CYP1A2, while CYP1A2 formed more 8,9-EET. CYP2C9 also generated a peak with the retention time of 12-HETE. CYP2E1 generated .omega. - 1-OH arachidonic acid and, to a lesser extent, .omega.-OH arachidonic acid (ratio 2:1). A small amt. of epoxygenase activity was also detected for CPY2B6; its overall activity, however, was only about twice control levels. Activities of **CYP2A6**, 3A3, 3A4, and 3A5 were low and limited to the .omega.-/.omega. - 1-OH arachidonic acid peak; CYP2D6 was inactive. Microsomes prepd. from three individual human livers varied threefold in total arachidonic acid metab. For all three livers .omega.-OH arachidonic acid was the major product (up to 74% of total metabolites). Epoxygenase products constituted 14 to 28% of the total products; 60 to 83% of those were EET-diols, indicating that the human liver microsomes have substantial EET-epoxide hydrolase activity. 11,12-EET was the major EET for two livers and 14,15-EET for the third. The CYP2C **inhibitor** sulfaphenazole depressed human liver microsomal epoxygenase activity by 50% at 50 .mu.M, while .alpha.-naphthoflavone inhibited arachidonic acid epoxygenase activity by 27% at 2 .mu.M and by 32% at 10 .mu.M. Collectively, these findings suggest that human liver microsomal arachidonic acid metab. is catalyzed principally by CYP2C enzymes. CYP1A2, CYP2E1, and possibly **CYP2B6** are likely to play more minor roles, though their contribution may be enhanced by exposure to inducers of those enzymes. **CYP2A6**, CYP2D6, and CYP3A enzymes are unlikely to make any significant contribution. The studies suggest further that the CYP compn. of the liver may affect the arachidonic acid metabolite profile and in turn the cellular effects resulting from arachidonic acid metab.

ACCESSION NUMBER: 1995:697172 CAPLUS
DOCUMENT NUMBER: 123:105456
TITLE: Arachidonic acid metabolism by human cytochrome P450s 2C8, 2C9, 2E1, and 1A2: regioselective oxygenation and evidence for a role for CYP2C enzymes in arachidonic acid epoxygenation in human liver microsomes
AUTHOR(S): Rifkind, Arleen B.; Lee, Charis; Chang, Thomas K. H.; Waxman, David J.
CORPORATE SOURCE: Dep. Pharmacology, Cornell Univ. Med. College, New York, NY, 10021, USA
SOURCE: Arch. Biochem. Biophys. (**1995**), 320(2), 380-9
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Arch. Biochem. Biophys. (**1995**), 320(2), 380-9
CODEN: ABBIA4; ISSN: 0003-9861
AB The membrane-bound endogenous fatty acid arachidonic acid can be released from membranes by phospholipases and then metabolized to biol. active compds. by cyclooxygenases, lipoxygenases, and cytochrome P 450 (CYP) enzymes. In the liver the CYP pathway is the most significant. Liver CYP arachidonate products include epoxyeicosatrienoic acids (EETs) and monohydroxylated products (HETEs). The authors examd. metab. of [1-14C]arachidonic acid by a panel of 10 human CYP enzymes expressed in HepG2 cells. In the absence of expressed CYP enzymes, control HepG2 cell

microsomes generated only small amts. of .omega.- and .omega. - 1-OH arachidonic acid (ratio 2:1). Microsomes from HepG2 cells expressing CYP2C8, 2C9, 1A2, and 2E1 were 7-21 times more active than microsomes from the HepG2 controls. CYP2C8, 2C9, and 1A2 principally generated epoxygenase products; 36 to 48% were in the form of EET-diols, reflecting host HepG2 microsomal epoxide hydrolase activity. CYP2C8 and 2C9 formed more 14,15- and 11,12-EET than did CYP1A2, while CYP1A2 formed more 8,9-EET. CYP2C9 also generated a peak with the retention time of 12-HETE. CYP2E1 generated .omega. - 1-OH arachidonic acid and, to a lesser extent, .omega.-OH arachidonic acid (ratio 2:1). A small amt. of epoxygenase activity was also detected for CPY2B6; its overall activity, however, was only about twice control levels. Activities of **CYP2A6**, 3A3, 3A4, and 3A5 were low and limited to the .omega.-/.omega. - 1-OH arachidonic acid peak; CYP2D6 was inactive. Microsomes prepd. from three individual human livers varied threefold in total arachidonic acid metab. For all three livers .omega.-OH arachidonic acid was the major product (up to 74% of total metabolites). Epoxygenase products constituted 14 to 28% of the total products; 60 to 83% of those were EET-diols, indicating that the human liver microsomes have substantial EET-epoxide hydrolase activity. 11,12-EET was the major EET for two livers and 14,15-EET for the third. The CYP2C **inhibitor** sulfaphenazole depressed human liver microsomal epoxygenase activity by 50% at 50 .mu.M, while .alpha.-naphthoflavone inhibited arachidonic acid epoxygenase activity by 27% at 2 .mu.M and by 32% at 10 .mu.M. Collectively, these findings suggest that human liver microsomal arachidonic acid metab. is catalyzed principally by CYP2C enzymes. CYP1A2, CYP2E1, and possibly **CYP2B6** are likely to play more minor roles, though their contribution may be enhanced by exposure to inducers of those enzymes. **CYP2A6**, CYP2D6, and CYP3A enzymes are unlikely to make any significant contribution. The studies suggest further that the CYP compn. of the liver may affect the arachidonic acid metabolite profile and in turn the cellular effects resulting from arachidonic acid metab.

L15 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB A variety of chems., including triacetyloleandomycin (TAO), .alpha.-naphthoflavone (ANF), and diethyldithiocarbamate (DDC), are widely used as inhibitory probes for select individual human cytochrome P 450 (CYP) enzymes, despite the fact that the selectivity of these inhibitors has not been rigorously evaluated. In the present study the authors take advantage of recent advances in cDNA-directed human P 450 expression to evaluate directly the P 450 form selectivity to TAO, ANF, and DDC, using a panel of 10 individual cDNA-expressed human P450s. Under exptl. conditions known to yield maximal TAO complexation with P 450 hemoproteins, TAO (20 .mu.m) inhibited the catalytic activity of expressed CYPs 3A3, 3A4, and 3A5, whereas it did not affect CYPs 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, or 2E1 activity. ANF inhibited not only CYPs 1A1 and 1A2 (IC50 = 0.4-0.5 .mu.m), but it was also similarly effective against CYPs 2C8 and 2C9. Increasing the concn. of ANF to 10 .mu.m led to inhibition of **CYP2A6** and **CYP2B6**. Although a previous study suggested that DDC is a selective **inhibitor** of CYP2E1, the present investigation shows that at concns. required to inhibit CYP2E1 (IC50 .apprxeq.125 .mu.m when preincubated with NADPH), DDC also inhibited CYPs 1A1, 1A2, 2A6, 2B6, 2C8, 3A3, and 3A4. Decreasing the concn. of DDC to 10 .mu.m, however, led to inhibition of **CYP2A6** (65% inhibition) and **CYP2B6** (50% inhibition), but none of the other P450s examd., including CYP2E1. Overall, these results establish that (a) TAO is a selective **inhibitor** of the human CYP3A subfamily; (b) ANF potently inhibits CYP2C8 and CYP2C9, in addn. to CYPs 1A1 and 1A2; and (c)

DDC cannot be employed as a diagnostic inhibitory probe for CYP2E1.

ACCESSION NUMBER: 1994:528496 CAPLUS
DOCUMENT NUMBER: 121:128496
TITLE: Evaluation of triacetyloleandomycin, .alpha.-naphthoflavone and diethyldithiocarbamate as selective chemical probes for inhibition of human cytochromes P450
AUTHOR(S): Chang, Thomas K. H.; Gonzalez, Frank J.; Waxman, David J.
CORPORATE SOURCE: Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Arch. Biochem. Biophys. (**1994**), 311(2), 437-42
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Arch. Biochem. Biophys. (**1994**), 311(2), 437-42
CODEN: ABBIA4; ISSN: 0003-9861

AB A variety of chems., including triacetyloleandomycin (TAO), .alpha.-naphthoflavone (ANF), and diethyldithiocarbamate (DDC), are widely used as inhibitory probes for select individual human cytochrome P 450 (CYP) enzymes, despite the fact that the selectivity of these inhibitors has not been rigorously evaluated. In the present study the authors take advantage of recent advances in cDNA-directed human P 450 expression to evaluate directly the P 450 form selectivity to TAO, ANF, and DDC, using a panel of 10 individual cDNA-expressed human P450s. Under exptl. conditions known to yield maximal TAO complexation with P 450 hemoproteins, TAO (20 .mu.m) inhibited the catalytic activity of expressed CYPs 3A3, 3A4, and 3A5, whereas it did not affect CYPs 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, or 2E1 activity. ANF inhibited not only CYPs 1A1 and 1A2 (IC50 = 0.4-0.5 .mu.m), but it was also similarly effective against CYPs 2C8 and 2C9. Increasing the concn. of ANF to 10 .mu.m led to inhibition of **CYP2A6** and **CYP2B6**. Although a previous study suggested that DDC is a selective **inhibitor** of CYP2E1, the present investigation shows that at concns. required to inhibit CYP2E1 (IC50 .apprxeq.125 .mu.m when preincubated with NADPH), DDC also inhibited CYPs 1A1, 1A2, 2A6, 2B6, 2C8, 3A3, and 3A4. Decreasing the concn. of DDC to 10 .mu.m, however, led to inhibition of **CYP2A6** (65% inhibition) and **CYP2B6** (50% inhibition), but none of the other P450s examd., including CYP2E1. Overall, these results establish that (a) TAO is a selective **inhibitor** of the human CYP3A subfamily; (b) ANF potently inhibits CYP2C8 and CYP2C9, in addn. to CYPs 1A1 and 1A2; and (c) DDC cannot be employed as a diagnostic inhibitory probe for CYP2E1.

L15 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB The present study identifies the specific human cytochrome P 450 (CYP) enzymes involved in hydroxylation leading to activation of the anticancer drug cyclophosphamide and its isomeric analog, ifosphamide. Substantial interindividual variation (4-9-fold) was obsd. in the hydroxylation of these oxazaphosphorines by a panel of 12 human liver microsomes, and a correlation was obtained between these 2 activities ($r = 0.85$, $P < 0.001$). Enzyme kinetic analyses revealed that human liver microsomal cyclophosphamide 4-hydroxylation and ifosphamide 4-hydroxylation are best described by a 2-component Michaelis-Menten model composed to both low Km and high Km P 450 4-hydroxylases. To ascertain whether 1 or more human P 450 enzymes are catalytically competent in activating these oxazaphosphorines, microsomal fractions prepd. from a panel of human B-lymphoblastoid cell lines stably transformed with individual P 450 complementary DNAs were assayed in vitro for oxazaphosphorine activation.

Expressed **CYP2A6**, -2B6, -2C8, -2C9, and -3A4 were catalytically competent in hydroxylating cyclophosphamide and ifosphamide. Whereas CYP2C8 and CYP2C9 have the characteristics of low Km oxazaphosphorine 4-hydroxylases, **CYP2A6**, -2B6, and -3A4 are high Km forms. In contrast, CYP1A1, -1A2, -2D6, and -2E1 did not produce detectable activities. Also, growth of cultured **CYP2A6**- and **CYP2B6** -expressing B-lymphoblastoid cells, but not of CYP-neg. control cells, was inhibited by cyclophosphamide and ifosphamide as a consequence of prodrug activation to cytotoxic metabolites. Expts. with P 450 form-selective chem. inhibitors and inhibitory anti-P 450 antibodies were then performed to detd. the contributions of individual P-450s to the activation of these drugs in human liver microsomes. Orphenadrine (a **CYP2B6 inhibitor**) and anti-CYP2B IgG inhibited microsomal cyclophosphamide hydroxylation to a greater extent than ifosphamide hydroxylation, consistent with the 8-fold higher activity of complementary DNA-expressed **CYP2B6** with cyclophosphamide. In contrast, troleandomycin, a selective **inhibitor** of CYP3A3 and -3A4, and anti-CYP3A IgG substantially inhibited microsomal ifosphamide hydroxylation but had little or no effect on microsomal cyclophosphamide hydroxylation. By contrast, the CYP2D6-selective **inhibitor** quinidine did not affect either microsomal activity, while anti-CYP2A antibodies had only a modest inhibitory effect. Overall, the present study establishes that liver microsomal CYP2B and CYP3A preferentially catalyze cyclophosphamide and ifosphamide 4-hydroxylation, resp., suggesting that liver P 450-inducing agents targeted at these enzymes might be used in cancer patients to enhance drug activation and therapeutic efficacy.

ACCESSION NUMBER: 1994:94956 CAPLUS
DOCUMENT NUMBER: 120:94956
TITLE: Differential activation of cyclophosphamide and ifosphamide by cytochromes P-450 2B and 3A in human liver microsomes
AUTHOR(S): Chang, Thomas K. H.; Weber, Georg F.; Crespi, Charles L.; Waxman, David J.
CORPORATE SOURCE: Dep. Biol. Chem. Mol. Pharmacol., Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Cancer Res. (**1993**), 53(23), 5629-37
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

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AB The present study identifies the specific human cytochrome P 450 (CYP) enzymes involved in hydroxylation leading to activation of the anticancer drug cyclophosphamide and its isomeric analog, ifosphamide. Substantial interindividual variation (4-9-fold) was obsd. in the hydroxylation of these oxazaphosphorines by a panel of 12 human liver microsomes, and a correlation was obtained between these 2 activities ($r = 0.85$, $P < 0.001$). Enzyme kinetic analyses revealed that human liver microsomal cyclophosphamide 4-hydroxylation and ifosphamide 4-hydroxylation are best described by a 2-component Michaelis-Menten model composed to both low Km and high Km P 450 4-hydroxylases. To ascertain whether 1 or more human P 450 enzymes are catalytically competent in activating these oxazaphosphorines, microsomal fractions prepd. from a panel of human B-lymphoblastoid cell lines stably transformed with individual P 450 complementary DNAs were assayed in vitro for oxazaphosphorine activation. Expressed **CYP2A6**, -2B6, -2C8, -2C9, and -3A4 were catalytically competent in hydroxylating cyclophosphamide and ifosphamide. Whereas

CYP2C8 and CYP2C9 have the characteristics of low Km oxazaphosphorine 4-hydroxylases, **CYP2A6**, -2B6, and -3A4 are high Km forms. In contrast, CYP1A1, -1A2, -2D6, and -2E1 did not produce detectable activities. Also, growth of cultured **CYP2A6**- and **CYP2B6** -expressing B-lymphoblastoid cells, but not of CYP-neg. control cells, was inhibited by cyclophosphamide and ifosphamide as a consequence of prodrug activation to cytotoxic metabolites. Expts. with P 450 form-selective chem. inhibitors and inhibitory anti-P 450 antibodies were then performed to detd. the contributions of individual P-450s to the activation of these drugs in human liver microsomes. Orphenadrine (a **CYP2B6 inhibitor**) and anti-CYP2B IgG inhibited microsomal cyclophosphamide hydroxylation to a greater extent than ifosphamide hydroxylation, consistent with the 8-fold higher activity of complementary DNA-expressed **CYP2B6** with cyclophosphamide. In contrast, troleandomycin, a selective **inhibitor** of CYP3A3 and -3A4, and anti-CYP3A IgG substantially inhibited microsomal ifosphamide hydroxylation but had little or no effect on microsomal cyclophosphamide hydroxylation. By contrast, the CYP2D6-selective **inhibitor** quinidine did not affect either microsomal activity, while anti-CYP2A antibodies had only a modest inhibitory effect. Overall, the present study establishes that liver microsomal CYP2B and CYP3A preferentially catalyze cyclophosphamide and ifosphamide 4-hydroxylation, resp., suggesting that liver P 450-inducing agents targeted at these enzymes might be used in cancer patients to enhance drug activation and therapeutic efficacy.

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